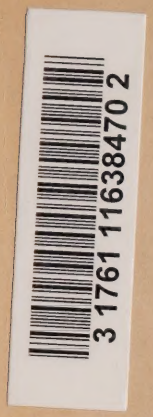


S U B M I S S I O N

on behalf of the

CANADIAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION

by

STANLEY NESBITT CONDER
General Manager

KING EDWARD HOTEL

before the

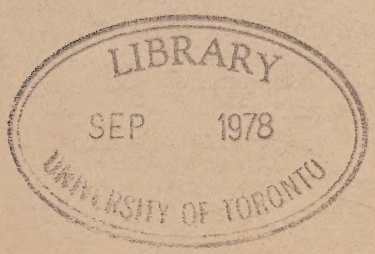
RESTRICTIVE TRADE PRACTICES COMMISSION
Department of Justice, Government of Canada

at

Toronto, Ontario

on

October 18, 1961



I N D E X

FOREWORD

Mr. Chairman and Members of the Restrictive Trade Practices Commission. This representation is being respectfully submitted to you on behalf of the Canadian Pharmaceutical Manufacturers Association.

I am Stanley Nesbitt Condor, General Manager of the Association. With me today is Brian Dixon, Ph.D., Assistant Professor, Commerce & Business Administration, Queen's University, Kingston, who is Economic Consultant to our Association.

Presented with this brief is an independent economic report on the pharmaceutical manufacturing industry, prepared by Dr. Brian Dixon. This economic report has been filed with your Committee in support of our representation, under Appendix C. Dr. Dixon is prepared to answer any questions concerning his report, following this presentation. In addition, we are including under Appendix D a copy of the submission which this Association made before the Ontario Government's Select Committee on Drugs in 1960.

INTRODUCTION

The Canadian Pharmaceutical Manufacturers Association was founded in 1914, and was incorporated under the Dominion Companies Act in 1959. It represents 56 companies engaged in manufacturing and distributing ethical pharmaceutical preparations in Canada. As the Commission is aware, the term "ethical" refers to pharmaceuticals dispensed on doctor's prescription and those not advertised to the public, as different from proprietary or patent medicines which are advertised to the public. As might be expected, some of our companies also make proprietary medicines to varying degrees, but our Association does not represent this field of medication.

An outline of our Association is appended to this representation under Appendix A, while a list of the membership is attached under Appendix B.

On behalf of our Companies, I wish to thank the Commission for giving our Association this opportunity to appear before you. We requested permission to make this representation with the hope that it will serve to engender a better understanding and appreciation of pharmaceutical manufacturing in Canada.

Erroneous reports to the contrary, this Association has not at any time made a request to your Commission for a private rather than a public hearing. In fact, we welcome a public hearing on the grounds that Canada's pharmaceutical manufacturing industry is operating in the best public interest, and that profits and manufacturers' selling prices are reasonable and consistent with good business practice.

As requested by the Commission, our basis for reference is the statement of material relating to the manufacture, distribution

and sale of drugs, prepared by the Director of Investigation and Research and referred to as the "green book".

Our remarks will be predicated on this statement of material.

The green book is an interesting summary of some aspects of pharmaceutical manufacturing in Canada and the author is to be complimented for the manner in which he clarified many of the intricacies of a most complex industry. As might be expected, we do disagree with certain comments and opinions which appear in the green book, particularly the use of hearsay evidence from domestic and foreign sources, but we realize that this was included not as a foregone conclusion but merely as an attempt to elicit more factual information.

We hope that our comments will not be mistaken as an all-encompassing criticism of what we are certain has been a time consuming task of considerable magnitude.

On the premise that the green book is not a report but a compilation of largely unsubstantiated material, we regret that it has been and is even now being looked upon in some quarters as an indictment of our industry by the Government of Canada. This is borne out by the press reports which were based on the green book during its initial public appearance. And upon the fact that some witnesses appearing before this Commission have used unsubstantiated statements from the green book as evidence in their own representations.

We further recognize that the Commission is aware of this situation, and that it will be considered in the preparation of the final report based on your findings. But we wish to offer this situation as prima facie evidence that the criticisms which have been

levelled at us are in many instances fostered by misunderstanding and opinion rather than fact and perspective.

In many cases the services being carried on by our industry as a major supplier to the medical profession have been distorted to the point where is has become almost fashionable to criticize drug costs and related factors.

Our companies are indeed doing an honest and conscientious job of supplying to Canadians the finest medication available, and their profits and prices are not out of line with the economic risks and costs involved in providing this service to the professions and the public.

Whatever the ultimate findings of this Commission, we hope and trust that the Commission's final report will at least help to alleviate the almost irreparable harm which has resulted unwittingly and unintentionally from certain statements contained in the green book.

A RESUME OF THE INDUSTRY

While Canada's pharmaceutical manufacturing industry was born in the middle 1800's, it did not gain a measurable economic stature until the post World War II years. It is within this past two-and-a-half decades, and the last one in particular, that pharmaceutical manufacturing has undergone a transition unprecedented in its history.

Penicillin marked the beginning. U.S. manufacturers operating under the emergencies of the war effort were called upon to find the means of mass-producing our first antibiotic, and to a lesser extent Canadian industry played its role in the exacting drama then unfolding. Ayerst set up one of the earliest known plants for penicillin production. In fact, it supplied the first Canadian-made penicillin to our Armed Forces, closely followed by Connaught and later

by Merck. These three provided Canada with penicillin long before it was available from any other source.

Other Canadian firms followed suit and when Sir Alexander Fleming came to North America in 1945, he paid tribute to the Canadian industry's part in the development of the product he had discovered:

"Penicillin has had a romantic career. It was born in a culture plate where it wasn't wanted and it was developed in the worst of all wars. I thank Canadian manufacturers for their share in this great work . . . three months ago Canada was ahead of the U.K. in the production of penicillin. You have done very fine work under difficult circumstances". 1/

The resulting evolution in the field of therapeutic substances brought with it a phenomenal growth in the size and operating capacity of the manufacturing plants, to meet the need for increased production to supply the medical profession with the new tools of discovery. Almost overnight, in terms of industrial development, the industry in North America changed from a commercial nonentity to one of the most vital factors in the health of the people.

Companies such as Lederle, Parke Davis and Pfizer which had introduced Aureomycin, Chloromycetin and Terramycin respectively, were entering a new period of development and growth. Wholly-owned Canadian companies such as Frosst and Horner, were also investing their reserves in research facilities to maintain their positions in the market, on the premise that no company can hope to survive without access to research.

The boom in growth produced economic hazards for the companies which were only coming to learn that theirs was a risk industry. New discoveries were rewarding, but the cost of research and

development was high. Lilly lost $850,000 on but one research failure, while SKF underwrote $750,000 on another. In 1958 alone, the pharmaceutical industry in North America worked on 114,600 different chemical substances in its laboratories. Less than 40 reached the market. 2/

Still the North American market for pharmaceuticals grew. Upjohn built a new manufacturing plant at Don Mills, Parke Davis built at Brockville and Pfizer at Arnprior. Hoechst opened a Canadian company to handle its then revolutionary oral anti-diabetic. Ortho built at Don Mills, while Ciba and Sandoz moved to larger facilities at Dorval. Wyeth at Windsor and BDH at Toronto made extensive plant additions. Other established companies followed suit, and still newer firms entered the Canadian market, adding to employment and the Canadian economy.

Competition via discovery became stiff. Formerly a leader in the corticosteroid market, Schering's earnings on this continent suddenly dropped 23 per cent in two years, when three other major competitors entered the field. The price of penicillin on the world market had become so low, that companies in Canada stopped producing the raw substance. Merck was forced to close its multi-million dollar penicillin, streptomycin and cortisone plant outside Montreal, as a result of imports from low cost countries, and some 400 Canadians were out of jobs. As a result of competition at the manufacturers' level, reserpine underwent a drastic drop in price within 18 months of its introduction to the Canadian market.

At the end of its second decade of rapid development, the industry's phenomenal growth is levelling off. Research is not producing as many new discoveries, and the companies are placing more

and more money into research with the hope of breaking the barrier to still another new molecular substance which, in turn, will produce a further upsurge in growth. Allied to this is the development of new drugs to compete with other drugs which, although different in content, are used for the same medical purpose.

Prices are continually being trimmed to compete with different products in the same therapeutic class, and with similar products held under compulsory or voluntary license by competitors. Patents are no longer a protective factor in marketing, although they still remain the primary incentive to research. Average profit margins are gradually narrowing, partly as a result of industry growth and partly through increased operating costs.

While retail prices remain relatively stable, manufacturers are becoming more and more concerned with the trend of their net earnings. Large companies presently doing at least 94 per cent of their manufacturing in Canada are continually examining the potential for the other six per cent.

With the swinging of the competitive pendulum, one company recently announced the construction of a multi-million dollar primary antibiotic plant in Southern Ontario. The chemical industry, suppliers of raw materials for the manufacture of pharmaceuticals, is also carefully watching the population growth which forecasts markets sufficient in size to warrant establishing primary producing plants in Canada.

Provided Canada continues to grow and prosper, and the industry is permitted to expand through logical development, the future is bright. But there is an overcast on the horizon. For there are

pressures in favour of importing drugs from abroad, which could result in removing the incentive for domestic manufacturing and the loss of employment to thousands of Canadians.

During the first six months of 1961, the cumulative monthly sales of pharmaceuticals in Canada was down 11 per cent over the previous year. Sales of ataractics, which represent about six per cent of the total market were off six per cent while antibiotic sales, representing about 10 per cent of the market, were down 12 per cent during this six month period. 3/

There is no doubt that our pharmaceutical manufacturers can cope with market trends and narrowing profits through competitive efficiencies, and so continue to provide for Canadians the finest medication available at a reasonable price well within the average Canadian's purchasing ability. But it can only do so if its future remains unfettered, and the decisions relating to this future are based on accurate understanding of the industry's accomplishments and role in the economy of the nation.

To present the facts as they apply to pharmaceutical manufacturing, we will deal first with the industry itself.

THE INDUSTRY IN GENERAL

While the green book uses Dominion Bureau of Statistics' figures for manufacturing for the years 1957 and 1958, against results of its own survey for the year 1959, DBS has since published its annual report for the year 1959.

According to the 1959 report, the industry comprised 188 companies engaged in manufacturing both ethical pharmaceuticals and proprietary medicines, a decline of eight companies from the previous year.

Many of these 188 firms are small regional concerns, while others manufacture proprietary preparations exclusively. It has been estimated, however, that about 70 of them are multi-line ethical pharmaceutical manufacturers, as we understand the term, about 75 are multi-line proprietary manufacturers, while the balance are agents, wholesalers and retailers who also manufacture some medicinals plus packaging concerns and other suppliers. Furthermore, this list does not include two major companies which manufacture ethical pharmaceuticals in Canada, and which are members of our Association.

The 188 companies listed by DBS shipped during 1959 a total of $164,733,036 worth of pharmaceuticals, proprietaries and certain other lines such as toiletries which are a secondary part of their business. It shows the actual production in Canada of medicinals, pharmaceuticals and biologicals for 1959 at $154,334,000 plus imports of $32,428,000, for a total of $186,762,000. It is further estimated that proprietary medicines account for approximately 22 per cent of this total which means that Canadian manufacturers and importers supplied in the neighborhood of $145,674,360 worth of ethical pharmaceuticals and biologicals for both human and veterinary use in 1959.

According to DBS, the gross selling value of medicinal and pharmaceutical products shipped by manufacturers in Canada increased 6.3 per cent from 1958 to 1959. Similarly, imports reached an all-time high in 1959 with a 10.9 per cent increase over 1958. Exports declined 29.3 per cent from $9,560,000 in 1958 to $6,758,000 during the same period.

Based on the shipment figure of $186,762,000, imports were about 17 per cent of the total for the year. This is significant

in light of the various statements in the green book which have created, and we believe unintentionally, the misconception that the large percentage of ethical pharmaceuticals are imported.

If we discount the importers, and there are a large number of these in Canada, the percentage of imports by ethical manufacturers is extremely low in relation to Canadian production. This is further borne out by a survey of 28 companies which we undertook in 1960, indicating clearly that these firms manufacture in Canada 94 per cent of their products, and import only six per cent. 4/

Nor was there any significant difference according to financial control. The wholly-owned Canadian firms manufacture 98 per cent of their products in Canada; the U.S. subsidiaries, 92 per cent; and the European subsidiaries, 94 per cent.

The firms covered in this survey were manufacturers and not merely distributing companies. In another survey of 40 firms, which included non-manufacturing members, we found that 81.5 per cent of the total sales volume was manufactured and packaged in Canada, 11.8 per cent was made outside Canada but packaged here, while 6.7 per cent was manufactured and packaged in other countries. 5/

In another example, the green book refers, on page 226, to the manufacture of "basic" antibiotics and ataractics and that "it is clear that most are imported into Canada." If this refers to the raw materials used in manufacturing, then this is correct. However, it is interesting to note that while the DBS annual report does not separate ataractics from its total volume, it does show that in 1959, $20,813,894 worth of antibiotic preparations were "made in Canada," a figure which cannot be far from the total Canadian market even though imports are not included.

Confusion in this respect has undoubtedly been created by the various references to drugs, pharmaceuticals, chemicals, basic drugs, dosage forms, and other similar wording. When the term drugs or pharmaceuticals is used in this industry it refers to dosage forms or the final product prescribed by the doctor and dispensed by the pharmacist. The gross selling value of products at the manufacturing plant, used by DBS, refers to products in dosage form and not to raw materials.

Pharmaceutical chemicals are raw materials to this industry. In a few cases, a chemical may be a drug but not all drugs are chemicals. Raw chemicals or active ingredients may be imported, but where the actual compounding into dosage form is done here then this compounding constitutes manufacturing.

It is an unfortunate fact that a large percentage of the raw materials used in this industry must be imported. The market for pharmaceuticals in Canada is not yet large enough to support a complete raw materials industry. The volume in dosage form is still too low to permit effective competition in many raw materials with suppliers in large volume markets such as the U.S., U.K., Italy or Japan, to name but a few. The time will come when it will be economical for our chemical industry to establish a complete raw materials division for our industry. In the meantime, Canadian pharmaceutical manufacturers must import many of their raw materials so that they can continue to manufacture drugs and place them on the market at the lowest possible price.

As an Association, we are primarily interested in manufacturers, although we do have some members which are importing

subsidiaries. Nevertheless, 83 per cent of the pharmaceuticals sold in Canada are manufactured here and many of our member companies are making more than 90 per cent of their products in this country.

To iterate, when reference is made to drugs and pharmaceuticals, it covers the end product and not the raw materials which go into that product.

In reference to Canadian manufacturing, DBS shows that our manufacturing plants employed 8,146 Canadians in 1959, at a total wage bill of $31,133,539. That was two years ago. Considering the manufacturers not included in this total and the many importers who maintain packaging operations here, it is estimated that total employment in this industry is now in the neighborhood of 10,000 and that salaries and wages paid to these employees is at least $39,000,000.

Attached to this submission, under Appendix C, is a copy of the economic report on our industry which Dr. Brian Dixon of Queen's University prepared in 1960. This report points out that wage payments per worker in pharmaceutical manufacturing have risen more rapidly than for the manufacturing group as a whole, which reflects the comparatively large proportion of skilled personnel required in this industry.

It is significant that during the past 12 years, salaries and wages have increased by more than $15,000,000. Furthermore, the employees represent some 10,000 households and, according to a formula developed by the CNR research department (6/), they account for a total of about 22,000 jobs as a result of their bearing on construction, transportation, communications, finance,insurance, utilities and other services. Granted, the industry is a small one in comparison to some

of our large durable goods industries, but there can be no doubt that pharmaceutical manufacturing is making a worthwhile contribution to employment and the national economy.

The DBS annual report also indicates that no mere handful of companies controls the pharmaceutical and medicinal manufacturing business in Canada. In 1959, 50 firms accounted for 89 per cent of the business, as compared to 53 companies representing 90 per cent in 1958. The remainder of the business was shared by 138 firms in 1959 as against 143 firms in 1958.

This ratio has remained fairly constant since 1955, and the status quo plus the large number of small companies in the industry is further evidence that there is no monopoly of the pharmaceutical market in Canada. Also, these low-volume firms while small in relation to the national companies, are often regional in character with sales volumes in their respective areas often higher than those of the larger firms.

As we have shown, sales of antibiotics and ataractics were down an average of about nine per cent during the first six months of 1961. This is a significant decline for any market, and is indicative of the need for product diversification in pharmaceutical manufacturing. The green book bases many of its conclusions on the results of the antibiotic and ataractic market, which only represents about 16 per cent of the total market. Antibiotics and ataractics are not necessarily typical of this market. If anything,they are atypical, and any attempt to pre-judge pharmaceutical manufacturing on the basis of these two products alone is bound to produce grievous errors.

To retain its position in the Canadian market, a company

must spread its cost over many products. It could not take the chance of limiting itself to one major field such as ataractics or antibiotics.

As is noticeable from the overall decline in antibiotics and ataractics this year, companies are constantly faced with a fluctuating rise and decline in sales from product to product. A company may conceivably find itself in first or second place in antibiotic sales this year. Next year, it might be in fifth or sixth place. If a competitor brings out an improved product in the same therapeutic class, its sales are bound to affect those of the first company. Accordingly, the first company must have some other major products to help carry the loss to its antibiotic sales. Plummeting sales of a large-volume product can materially change a company's entire financial picture.

For this very reason, it is not practical to base a company's entire operations on one or two products, such as antibiotics or ataractics. We must base our findings on the company's overall operations, and this is equally true at the industry level. This was borne out in the recent survey referred to earlier. Thirty-five companies indicated the following:

10 make both antibiotics and ataractics;

12 make antibiotics but no ataractics;

5 make ataractics but no antibiotics;

8 make neither antibiotics nor ataractics.

Thus, 20 of these 35 firms make no ataractics, while 13 make no antibiotics, and these are all major companies in the industry. 7/

Allied to this product diversification, is the fact that

many pharmaceutical manufacturers carry "public service" products on which they actually lose money or break even on cost. Some of these drugs are actually given away free. These are largely products discovered in pharmaceutical laboratories which have a limited use in that they are often for rare diseases or ailments.

In many cases these "public service" products are the result of extensive research, but for a variety of reasons have a small demand. Aldosterone is an excellent example. Used to combat diminished or absent adrenal function, this mineralocorticoid was isolated and synthesized by Ciba. While of major physiological importance, it has as yet a limited therapeutic use.

Few Canadians have cause to fear venomous snakes in this country. Yet the occasional near fatality does occur, and it is for this reason that Wyeth maintains a stock of Antivenin, the anti-snake bite serum. Roche, on the other hand, produces a chemotherapeutic agent called 5 FU. Administered in the treatment of certain cancers, it is given free to qualified clinicians.

Warner-Chilcott did considerable research on Releasin, only to find that it is extremely difficult and costly to manufacture. Initially used in threatened abortion, it has now been found helpful in alleviating scleraderma, a rare disease causing hardening of the skin and for which there is no known cure. The company loses money every time it makes a sale of this product.

Mead Johnson's Lofenalac is truly a life-saving boon to sufferers of phenylketonuria. This is a rare disease of children which, if untreated, will eventually cause permanent and fatal damage to the brain. Fortunately, this disease can be easily detected and, if

determined in the early stage, Lofenalac will actually prevent the brain damage, permitting the child and later the adult to live a normal life. This is the only product of its kind available in Canada. Yet Mead Johnson makes it available at cost, taking no profit whatever on the product.

While products such as these are not commercially profitable, companies keep them in stock for humanitarian reasons. In most cases, the use is so limited that the so-called prestige value bears no relationship to the cost involved.

A recent survey of 39 companies indicated that 22 of these firms carry products of this type. 8/ During 1960, these 22 manufacturers supplied a total of 112 public service products at a total volume of about $400,000 for an average of some $3,571 per product for the year. One company with 10 such products reported that its individual product sales ranged from 19 to 7,540 packages during the 12 month period.

Other factors must also be considered when judging the efficiency and effectiveness of this industry, such as the guaranteed sales policy which is almost unique to pharmaceutical manufacturing. This is where the company agrees to take back for credit or exchange, products which for some reason or other are not used or sold. It will be appreciated that pharmaceuticals are vitally important to the health of the patient, and it is essential that the supplies on retail shelves be maintained in peak condition. If it were not a policy of manufacturers to accept returned goods for credit, retailers and wholesalers would be forced to either refuse to maintain adequate stocks, or resort to higher prices to compensate for the additional cost involved.

As practices appeared to vary from company to company on this subject, we conducted a survey of member companies to provide a consensus for this submission. 9/ Of 39 companies which replied:

1. 38 permit the return of goods from hospitals, for full credit.

   1 accepts returns from hospitals for partial credit.

2. 35 permit the return of goods from government departments for full credit, although one qualified this by adding "if not on contract".

   1 stated "provincial hospitals only".

   2 accept such returns for partial credit.

3. 39 permit the return of goods from wholesalers for full credit.

4. 38 permit the return of goods from retailers for full credit.

   1 accepts such returns for partial credit.

One company added the note that "our returned goods result in about 4 per cent of our sales in any calendar year". Another company stated that partial credit may be given instead of full credit, depending on age and condition of the material returned.

Regarding retailers, most companies will accept back unopened packages regardless of the condition of the package, but the majority will not accept returns for full credit where the package has been opened.

Thirty-six of the 39 accept returns of obsolete products when they have been replaced by newer products. Twenty do not specify a time limit within which the product must be returned for credit, but 19 do specify a time limit which in most cases is considered liberal. This, of course, would depend in some cases upon the number of undated products on the company's list. Some companies authorize their

detailmen to take back an opened package and replace it with a product of approximately the same value, but this practice is not prevalent.

We also asked the companies what they do with returned goods and 35 replied that they generally destroy such returns. However, many companies will attempt to salvage returns provided that the material is not dated, is of recent manufacture, and the container is only damaged or soiled. This applies primarily to tablets, and such returns must first be approved by the quality control laboratory.

In respect to marketing, one witness before this commission referred to companies insisting that non-prescription products be sold only on prescription. This point subsequently has arisen many times during the Commission's cross-examination of witnesses. Accordingly, we asked our companies this question: "Have you at any time insisted that non-prescription items be sold only on prescription at the retail level." The 39 companies which replied to this survey all stated "no". 10/

One company qualified its negative reply, by first stating that it has never insisted that this be done, but adding that it may have dissuaded a retail pharmacist from selling a non-prescription product over the counter: "As an example, if we were asked by a retail pharmacist if one of our antihypertensive agents could be sold over-the-counter, our answer would be that it could be sold legally. But since it is a potent substance which is used in the treatment of a serious ailment, we would suggest that in the patient's interest, it would be preferable that a physician be consulted."

Another company followed this example in 1956 during introduction of a new and highly potent ataractic of the perphenazine

family. In view of extrapyramidal symptoms involved in this drug, the dosage had to be carefully adjusted to the patient according to recommended maximums. This company felt that the drug should be used only under a physician's supervision, but ataractics were not officially classified as prescription drugs at that time. For this reason, the company discouraged over-the-counter sale of this product until it and other ataractics were eventually placed on the prescription list.

The final decision was, of course, left to the pharmacist's discretion, and it is generally accepted that our companies do not and can not insist that non-prescription items be sold on prescription.

To assist the Commission in its deliberations, we are including on the following three pages tables showing a breakdown of the average sales dollar of 40 companies for the year 1960, and an analysis of the sales dollar in percentages for the years 1958, 1959, and 1960.

It will be noticed that profits after taxes in 1960 were 5.5¢ of the sales dollar, as compared to 4.4¢ for all manufacturing industry. Compare this 5.5¢ profit with the 11.7¢ which was paid out in excise, sales and income taxes for the year.

More than one-quarter of the total sales dollar, or 26.2¢ went towards wages, salaries and employee benefits, while materials used in manufacturing accounted for 28.7¢. Comparing expenses to profits, it cost our pharmaceutical manufacturers 94.5¢ for every dollar's worth of merchandise sold in 1960.

As will be seen from the table covering percentages for the three-year period, the portion of the sales dollar allocated to wages and salaries increased from 1958 to 1960, while that for all

manufacturing decreased. In line with the national average, the cost of materials used in manufacturing has steadily declined. Excise and sales taxes, on the other hand, have steadily risen. The ratio of taxes on income to profit has gradually narrowed to the point where it is now even.

While the breakdown of the sales dollar naturally varies from industry to industry, it is significant from the Canadian Manufacturers Association's comparison, that pharmaceutical manufacturing is not out of line with the average for all manufacturing. The comparisons for the year 1960 indicate that our cost of materials is not as high as that for all industry. While our profit after taxes is 1.1 higher than the national average, it is significant that a greater percentage of our sales dollar goes towards wages and salaries, and taxes.

RESULTS OF THE STATISTICAL SURVEY FOR THE YEAR 1960

The following is the result of a survey of 40 pharmaceutical manufacturing companies, undertaken on behalf of C.P.M.A. by Clarkson Gordon & Company, Toronto. 11/

	Dollar Value	Percentage
1. NET SALES (That is, gross sales including sales tax where sales are made tax included, less returns and allowances):		
a. HUMAN PHARMACEUTICALS (Incl. all vitamins and O-T-C pharmaceuticals):	$107,929,000	84.2%
b. VETERINARY PHARMACEUTICALS:	2,029,000	1.6%
c. PROPIETARY MEDICINES (Patent medicines but not O-T-C pharmaceuticals):	826,000	0.7%
d. CHEMICALS:	7,346,000	5.7%
e. OTHER PRODUCTS (not listed above):	8,237,000	6.4%
TOTAL NET SALES:	126,367,000	98.6%
f. NOTE: participants reported that they manufactured $3,021,000 worth of merchandise for other C.P.M.A. members, including $2,791,000 of human pharmaceuticals.		
g. OTHER INCOME:	1,836,000	1.4%
TOTAL INCOME: (Comprising a, b, c, d, e and g, and including sales tax):	$128,203,000	100.0%
2. WAGES AND SALARIES (All wages and salaries including management salaries, directors' fees, payments to employees for holidays and in connection with profit sharing or production incentive plans, unless such payments are distributed only upon retirement of employee or some other similar basis, in which case they are included in 3.):	31,183,000	24.3%

3. EMPLOYEE BENEFITS (Payments to pension plans, group life, sickness or hospitalization insurance, workmen's compensation, unemployment insurance, medical services, cafeterias, welfare funds, 25-year clubs, etc.):	2,396,000	1.9%
4. MATERIALS (Including raw materials, finished and semi-finished materials, purchased for resale, materials consumed in processing operations, and packaging and shipping materials, but not plant supplies which are included in 6.):	36,765,000	28.7%
5. EXCISE AND SALES TAXES (Include in 1. above, remitted or to be remitted to Dominion and other governments):	8,021,000	6.2%
6. OTHER EXPENSES (Including plant supplies, power, water, municipal taxes, maintenance, repairs to buildings, machinery and equipment (not including salaries and wages or employee benefits included in 3. above), office, administrative and selling expenses not included above, including charitable and interest expense):	33,613,000	26.2%
7. DEPRECIATION:	2,157,000	1.7%
8. TAXES ON INCOME (Dominion and provincial taxes on income):	7,063,000	5.5%
9. PROFIT (Including profits distributed and amount retained in the business):	7,005,000	5.5%
TOTAL (Comprising 2 to 9 inclusive):	$128,203,000	100.0%
10. NUMBER OF EMPLOYEES (Average over 12-month period of fiscal year):	5,950	
11. TOTAL NET WORTH (Capital stock - preferred common etc. - and total retained earnings - surplus and reserves):	$ 57,800,000	

ANALYSIS OF THE SALES DOLLAR IN PERCENTAGES FOR 1958, 1959 AND 1960

The following shows the breakdown of the sales dollar in percentages for pharmaceutical manufacturing companies in the years 1958, 1959 and 1960. The number of companies involved and the accounting firms retained to compile returns to these surveys are as follows:

YEAR	NO. FIRMS REPLYING	SURVEY HANDLED BY
1958	28	John S. Entwhistle & Co., Toronto.
1959	43 12/	Henry Glover & Co., Toronto.
1960	40 13/	Clarkson Gordon & Co., Toronto.

The percentage figures in brackets below are the results of the Canadian Manufacturers Association survey for all manufacturing industry in Canada, and are included for comparison. For further information on headings see details shown under headings of the dollar volume tabulations on the preceding pages.

	1958	1959	1960
1. NET SALES FOR:			
a. Human Pharmaceuticals	80.5% (99.2)	73.8% (98.8)	84.2% (98.7)
b. Veterinary Pharmaceuticals	1.4%	1.6%	1.6%
c. Proprietary Medicines	1.0%	2.9%	0.7%
d. Chemicals	3.8%	7.6%	5.7%
e. Other Products	12.2%	12.9%	6.4%
f. Other Income	1.1% (0.8)	1.2% (1.2)	1.4% (1.3)
TOTAL	100.0%	100.0%	100.0%
2. WAGES AND SALARIES	23.7% (22.0)	22.8% (21.9)	24.3% (21.5)
3. EMPLOYEE BENEFITS	1.8% (1.6)	1.7% (1.7)	1.9% (1.7)
4. MATERIALS	32.7% (46.5)	32.3% (46.2)	28.7% (44.5)
5. EXCISE AND SALES TAXES	5.1% (3.5)	6.0% (3.0)	6.2% (4.7)
6. OTHER EXPENSES	23.2% (14.2)	23.4% (13.4)	26.2% (15.2)
7. DEPRECIATION	1.5% (4.0)	1.6% (3.6)	1.7% (4.1)
8. TAXES ON INCOME	5.5% (3.6)	6.0% (4.2)	5.5% (3.9)
9. PROFIT	6.5% (4.6)	6.2% (5.1)	5.5% (4.4)
TOTAL	100.0%	100.0%	100.0%

As we mentioned earlier, our Association primarily represents companies which manufacture under their own names in this country, but we also include in our membership as Associate Members, non-manufacturing subsidiaries of foreign manufacturers which maintain adequate quality control facilities.

Most of our present Full Members which are subsidiaries of foreign corporations, originally started out on a small basis without Canadian production facilities. In time, their volumes eventually reached the point where it was economical to set up plants in this country.

Based on our experience in this area, we take issue with the statement on page 15 of the green book which opines that "importations from the U.S. do not assist in developing Canadian production facilities any more than do importations from other countries". As a flat statement, without qualification, this is incorrect.

It is an historical fact that U.S. importing subsidiaries have eventually established more manufacturing plants here than all other countries combined. In these cases, importations from the U.S. have resulted in developing Canadian production facilities to a greater extent than any other single source. Furthermore, the great majority of these subsidiaries are headed up by Canadian-born management who consider their operations wholly Canadian. This is offered merely as a matter of fact, for we hold no particular brief for U.S. subsidiaries over those of other countries in our Association's day-to-day operations.

The green book also states that "conditions in the drug

industry in Canada are influenced by conditions in the U.S." Having studied other secondary industries, the Commission realizes that this situation is not unique to pharmaceutical manufacturing. Virtually every facet of the Canadian economy is influenced by U.S. conditions, including our labour unions. Whether we like it or not, economic developments in Canada are strongly influenced by corresponding movements in the United States, and this is part of the price we must pay for our proximity to a much larger and more highly industrialized nation. Nor is this necessarily detrimental from the nationalistic viewpoint. The proximity, and resulting similarity between our two peoples, has helped us to achieve one of the highest standards of living in the world, and this standard is even higher than many regions in the U.S.

Regardless of where the money came from, Canada has now built for itself a strong and growing domestic pharmaceutical manufacturing industry which is largely self-sufficient at the secondary level. Eventually, even the primary raw materials will be made here, and when that day arrives we will have a complete and independent unit within the economy.

In the event of a major catastrophe, this industry would be even more vitally important to Canada. Should hostilities again break out, supplies would be cut off and this country would be required to fall back on its domestic facilities to meet the needs of our nation. Even now, our civil defence authorities at Ottawa are examining the locations of our manufacturing plants to determine which are in strategic areas. We certainly hope that a world conflagration will not arise from the present turmoil, but if it does then the nation will need a home-based industry more than ever before in its history.

Price may be a short-term factor in importing from abroad, but it is essential that we maintain our own pharmaceutical manufacturing industry, for the service it offers to the professions, for the employment it provides our people, for the taxes it adds to the government's coffers, for its general contribution to the economy in peacetime, and for its value as a strategic industry during hostilities.

PRICES

Much has been said about the so-called high prices of drugs, and even the author of the green book apparently takes it for granted that prices of drugs are high. But "high" in what respect? The word price itself is relevant. An automobile is high in price compared to a loaf of bread. A pair of shoes costs more in Canada than in Italy, but the Italian labourer must work more hours than the Canadian to earn the money with which to buy them.

Economists in retail pharmacy have shown that in 1959, 46.3 per cent of the prescriptions dispensed in Canada were priced at $2.00 or less, while 58.8 per cent were under $3.00, and 88.6 per cent under $5.00. Only 1.1 per cent cost more than $10.00. 14/ Granted, this does not tell us whether drugs are reasonably priced. But neither does it indicate that our companies are making excessive profits. The only effective means that we have of weighing this price factor is to apply it against the usual economic indicators, the most common of which is the Federal Government's Consumer Price Index.

From 1949 to 1960, the consumer price index for prescription drugs increased only 12.9 per cent and was, at the end of 1960, one of the lowest items in the overall consumer price index, as is shown by the following:

CONSUMER PRICE INDEXES - MAJOR GROUPS 15/

Classification	1949-60
All Consumer Items	128.0
Food	122.2
Housing	132.7
Transportation	140.3
Recreation	141.6
Prescription Drugs	112.9

Obviously, the increase in the price of prescription drugs has not been as great as many items such as food and housing which are as vital to the health and well-being of Canadians as drugs. Furthermore, the following, according to DBS figures, shows that the price of drugs has not increased as much as health care costs in general:

CONSUMER PRICE INDEXES - HEALTH CARE 15/

Classification	1949-60
Health Care	158.7
Doctors' Fees	143.6
Dentists' Fees	154.8
Optical Care	131.6
Confinement	155.4
Prepaid Medical Care	172.6
Prescription Drugs	112.9

It is evident that during the 11 year period ending 1960 drug prices in Canada showed a smaller increase on the consumer price index than any other single element of health care.

The next step is to determine whether Canada's health care costs are in line with those of other countries. The following chart compiled from a study undertaken by the International Labour Organization and covering the year 1955 shows at that time total medical care costs, based on average income and purchasing ability, were lower in Canada than in the United States, United Kingdom, France, Norway, West Germany, Belgium and Italy, as follows:

MEDICAL CARE COSTS BASED ON INCOME AND PURCHASING ABILITY 16/

Country	Cost Factor
West Germany	2.15%
France	1.98
Norway	1.91
United Kingdom	1.87
Denmark	1.82
United States	1.79
Belgium	1.70
Italy	1.66
CANADA	1.57
Netherlands	1.51

Unfortunately, we were unable to obtain more current figures. However, as consumer price indices include health care, the following chart is submitted to show that consumer prices of most of these countries have increased more than that of Canada from 1953 to the third quarter of 1960:

CONSUMER PRICE INDEXES BY COUNTRY 17/

Country	Consumer Price Index
France	134
Netherlands	122
United Kingdom	121
Norway	121
Denmark	120
Italy	116
Germany	114
United States	111
CANADA	111
Belgium	110

Consequently, in chronological order:

1. Consumer prices of most other countries have increased more than those of Canada from 1953 to 1960.

2. In 1955, there was a lower proportion of income spent on medical care in Canada, than in most other countries.

3. Price of all other elements of health care increased more than that for prescription drugs from 1949 to 1960.

4. During this same period, prescription drugs have shown a smaller price increase than other essential non-health items required to sustain life.

The price economics of any product depend upon the conditions which, combined, make up the individual's standard of living. And per capita income is the measure of the individual's ability to afford the things which make up his standard of living. Canadians have one of the highest standards of living in the world, and there can be no doubt that this is adding to our costs in all areas of development.

As has been shown, the consumer price index for drugs increased only 12.9 per cent from 1949 to 1960. Yet it now costs our drug companies more to buy the materials with which to manufacture these drugs. Production and quality control equipment has increased in price. And, more important, the thousands of employees in our industry are making higher wages than ever before.

Average weekly wages in manufacturing in Canada increased some 78 per cent from 1949 to April 1961. 18/ This is far in excess of the comparable increase for prescription drugs and leaves but one conclusion: That the Canadian worker can better afford to buy drugs now than he could in 1949.

We further submit that the prices of drugs in Canada are actually low in relation to the comparable purchasing ability of the average Canadian. If a problem does exist, then it is with a small percentage of the population which, for reasons of substandard income or chronic illness, finds it difficult to purchase all commodities including drugs.

In addition, there are the relatively few cases where a long-term user of drugs, even though he is making an adequate wage, is faced with substantial medical bills for doctors' fees and drugs. For instance, the industry was incorrectly condemned in the House of Commons

for the cost of drugs required by the Dale children of Ottawa who are afflicted with cystic fibrosis. 19/ Not only were the costs submitted to the House incorrect, but several of our companies were actually at that time contributing free of cost to the Dale family the drugs required in this case.

There is no doubt that the small number of economic indigents in our population require serious consideration, but this is no indication of a high price of drugs any more than a family which cannot afford shoes for its children is an indication of a high price of footwear.

The average Canadian can well afford to meet his drug bill, and the comparatively few exceptions to this rule constitute a social problem to the nation rather than one of industry economics.

COMPARISONS OF PRICES IN OTHER COUNTRIES

The green book states that prices in Canada are "probably the highest in the world". This is obviously based on the publicity statement issued by the Kefauver Sub-Committee in the United States which criticized Canada on the basis of the now renowned chlorpromazine example. One product does not constitute a drug industry, nor do antibiotics or ataractics typify the economics of pharmaceutical manufacturing. In themselves, they are important therapeutic substances, but they represent only one facet of the industry's role in medicine.

Canadian drug prices are not necessarily the highest in the world, although there can be no doubt that Canada's standard of living is one of the highest in the world. The purchasing ability of the individual is the true indication of the reasonable price of any

product, and this indicator must be based on the number of hours of work required to buy the product. Low consumer prices invariably reflect low wages.

For example, the following table shows the number of hours a bricklayer requires to earn a 1 kg. loaf of bread in nine different countries.

TIME REQUIRED TO EARN 1 KG. OF BREAD IN VARIOUS COUNTRIES 20/
October, 1960

Japan, Tokyo	47.8 minutes
Italy, Rome	32.2 "
Germany, West Berlin	25.1 "
Argentina, Buenos Aires	20.2 "
Holland	16.6 "
Belgium, Brussels	16.4 "
United Kingdom	14.6 "
Canada, Toronto	7.3 "
U.S.A., New York	6.6 "

It has been further stated in the green book that the price between Largactil in Canada and Thorazine in the United States "reflects the usual relationship between Canadian and U.S. prices" (i.e., $6.25 to $5.05). There is a considerable variation in the prices of drugs between the two countries, as is shown by the table on the following page.

This table represents the products of 14 companies, which are sold in both the U.S. and Canada. From an average of 86 products, 16 were higher in the U.S. by 19 per cent, while 53 were higher in Canada by 13 per cent and this includes Canada's 11 per cent sales tax.

Comparisons of prices in Canada with those of other countries should only be made less the 11 per cent sales tax to obtain a proper differential when discussing the manufacturers' or retailers' operations. And when we use a discount of 10 per cent to approximate the 11 per cent tax included in the price of the product, we find some interesting facts.

DIFFERENCES BETWEEN DRUG COSTS IN CANADA AND THE U.S. 21/

	Total Products Compared by each Company	No. higher in Canada	by %	No. higher in U.S.	by %
	40	20	7%	8	10%
	26	17	20%	5	10%
	28	16	16.6%	12	4.4%
	120	75	16.8%	42	18%
	18	12	12%	3	11%
	57	50	11.5%	7	15.2%
	176	162	11.7%	14	32.3%
	90	77	16.8%	13	21%
	32	26	11%	6 (not incl.)	"Varies" (not incl.)
	213	0	0	1	40%
	124	112	19%	10	17%
	26	19	16.5%	5	22.5%
	145	109	11%	12	15%
	118	44	16.3%	74	32.6%
AVERAGES:	86	53	13%	16	19%

Percentage differences between list prices of Canadian and U.S. companies based on products sold in both countries.

For example, on page 203 of the green book there is a comparison of prices to druggists of prednisone for 10 countries. Using the footnote figure of $19.87, which is the more accurate of the two, and deducting sales tax, we arrive at a price figure for Toronto of $17.89. As shown in the following table, this means that the price of this product was lower in Canada than in the United States, Italy, Panama, Australia and Japan.

PRICES TO DRUGGISTS OF PREDNISONE, 1959

City and Country	Price to Druggist
Tokyo, Japan	27.78
Sydney, Australia	24.00
Colon, Panama	22.99
Rome, Italy	22.16
United States	17.90
Toronto, Canada	17.89 (less sales tax)
Vienna, Austria	17.16
Amsterdam, Holland	16.05
Rio de Janeiro, Brazil	14.15
London, England	7.53

The average price for all 10 countries is $18.76, which means that Canada's price is well below the average. And if we use the median as the basis for comparison, the price Canadians pay for this product is among the lower half of the 10 nations.

In another case, on page 206, we find a list showing the manufacturers' selling price to the druggist, of various brands of meprobamate. To avoid price differences among competing products, we will use Equanil for comparison which, less sales tax, would be sold to the pharmacist for $3.24, indicating the following comparison:

PRICES TO DRUGGISTS OF EQUANIL, 1959

Country	Price to Druggist
Venezuela	5.44
India	4.25
Iran	3.55
Australia	3.47
United States	3.25
Canada	3.24 (less sales tax)
France	2.65
Japan	2.56
Brazil	2.20
Mexico	1.80

Here we find that the average of the total for these 10 countries is $3.24, exactly the selling price to the druggist less sales tax, in Canada. Again the median indicates clearly that the Canadian price is among the lower half of these countries.

These two cases cover a steroid and ataractic, and are offered as evidence that manufacturers' prices of pharmaceuticals in Canada are not among the highest in the world. In fact, they compare most favourably with world prices.

However, as was pointed out earlier, two products do not make an industry. Pages 210-213 of the green book contain a list of 69 items showing a direct relationship between prices in Canada and those in the U.S. For this reference, we have used the revised figures for one of the products, perphenazine, subsequently submitted during the hearings by Mr. Macleod.

Removing the 11 per cent sales tax from the Canadian products, as this tax does not apply in the U.S., we find that of these 69 items:

The prices of 11 are even or within 3¢ of each other;

The prices of 30 are lower in Canada than in the United States;

The prices of 28 are lower in the United States than in Canada.

If hospital purchasing agents in the two countries bought all of these drugs for their respective hospitals at these prices, less sales tax, the total costs would be as follows:

United States	-	$1,589.97
Canada	-	1,641.35

The actual difference is only $51.38 or about 3 per cent higher in Canada, and this can be accounted for by differences between some 3 or 4 dosage forms representing a couple of products out of the 69. In view of the fact that it costs considerably more to do business in Canada than in the United States, it is surprising that this differential is not greater.

If anything, the price of pharmaceuticals in Canada should be higher than in the U.S., regardless of our sales tax, for the following reasons:

1. Most raw materials must be imported from the U.S. and other nations, at a cost of anywhere from 15 to 20 per cent more than that paid by the U.S. manufacturer for the same materials. The same applies to manufacturing equipment.

2. The Canadian market is less than 10 per cent the size of the U.S. market, and therefore not conducive to comparable mass production techniques.

3. About 17 per cent of all pharmaceutical and medicinal products sold in Canada are imported, thereby cutting down still further on the size of the domestic market for Canadian manufacturers.

4. Because of the widely dispersed Canadian market, the Canadian manufacturer must pay more in transportation and distribution costs than his U.S. counterpart.

For these reasons, per unit costs are higher in Canada than in the United States. We will not enlarge on these four points, for they are well recognized in this country. Further details may be

found in Appendix C of our representation to the Ontario Government's Select Committee on Drugs, a copy of which is attached.

PROFITS

It is accepted that in the free enterprise system which operates in Canada, the profit motive plays an important part. Profit is the reward for the use of capital and for the taking of risks. We assume that no one questions the right of the pharmaceutical manufacturers to earn a reasonable margin of profit in their business.

In the field of pharmaceutical manufacturing, profits have been the spur to research and development which has produced more new drugs in the past decade than in the preceding twenty centuries. These same profits have also enabled subsidiaries of foreign corporations to establish manufacturing plants in this country, thereby adding measurably to employment and the economic health of Canada.

The rate of profit considered reasonable for any particular industry will vary, depending upon the type and nature of that industry and its products. A company which has a stable product, with little competition and fairly constant volume of sales from year to year, can attract capital with a fairly low margin of profit. On the other hand, an industry which is new, or which is constantly changing, or which has products subject to style changes or rapid obsolescence for one reason or another, will require a higher margin of profit in order to attract capital.

We submit that in this industry there is a high degree of financial risk, in that a product may become obsolete overnight with the introduction by a competitor of a more effective therapeutic substance. The life span of a drug may be comparatively short and the company must

necessarily take this into account. As competitive products appear, sales of the corresponding product by the company will gradually account for a smaller percentage of the market. It must then switch its emphasis to other products, or find a new product to replace the one which has become obsolete. In addition to taking into account this risk factor, a company must assume that its high volume products will support its low volume products.

The fact that there is a high degree of risk in the pharmaceutical business is borne out by the percentage of loss companies in this industry which, over the six year period ending 1958, was higher than that for the average of all manufacturing industries. In a sampling of ten selected industries during the same period pharmaceutical manufacturing, in number of losses sustained, was second only to that of machinery manufacturing. We suspect that much of the misunderstanding concerning pharmaceutical manufacturers' profits has resulted in publicity emanating from the United States regarding mark-ups on drug products reputed to be in thousands of percent. This has perhaps created the illusion that the spread between raw material costs and suggested list prices is pure profit to the manufacturer. This is completely unrealistic and unsound and ignores all the costs of manufacturing and selling the product, quite apart from the development and research costs that may be involved and the tax that may be levied against the company. It is our submission that the profits generated by the pharmaceutical manufacturers in Canada are in fact fair and reasonable.

In the reference to profits in the green book, rates of return are shown on pages 147 and 151 in the form of profits before

taxes as an indication of the "profit on sales". We think it more realistic to look to the real earnings of the company as the profits after income taxes have been paid. In the table submitted earlier in this brief it was shown that for 1960, 40 pharmaceutical manufacturers taking part in our survey had combined profits after taxes of 5.5 per cent of sales. Similar figures for 1958, 1959 and 1960 compared with averages for all manufacturing industries published by the Canadian Manufacturers Association are as follows:

YEAR	CPMA	CMA
1960	5.5%	4.4%
1959	6.2%	5.1%
1958	6.5%	4.6%

While the C.P.M.A. figures were compiled from annual surveys of our member companies, they nevertheless are indicative of the industry average. The Department of National Revenue in its publication of manufacturing statistics shows that the pharmaceutical industry in Canada made a profit after tax of 6.5 per cent for the year 1958, which corresponds with the result obtained in our survey. It is submitted that to anyone who has knowledge of profit margins, the average profit of the pharmaceutical manufacturing industry is not unreasonable and, in fact, for 1960 is only very slightly higher than that obtained for all manufacturing industries in Canada.

RESEARCH AND DEVELOPMENT

Since the dawn of time, man has sought to find a miracle substance which would cure disease and alleviate illness. Next to the alchemist's formula for synthetic gold, this was the greatest single aim of pre-dawn science and the men who practiced this art were looked upon with a mixture of awe and fear.

By the mid-centuries, this fear of the unknown had transcended reason to the point where our early researchers were accused of black magic and condemned by the laity.

It was not until the end of the 18th century that medical research won a modicum of recognition, and even then it was looked upon with suspicion. As recently as 100 years ago, the acceptance of medical research had not regained the complete freedom and respect it had won some 2,000 years earlier.

Then, with the turning of the 20th century, came the complete enlightenment essential to the furtherance of science. And scientific medicine eventually broke the barrier nature had erected around the molecular structure. Within the life span of everyone in this room, medical research has produced the greatest period of discovery in the history of man.

The term "wonder drug" was not an innovation of the pharmaceutical manufacturing industry. It was a coined invention of the press during the early days of the antibiotics, as a means of referring to the startling transition in medicine wrought by the steady stream of new therapeutic substances.

But memories are short-lived. We are prone to forget the limited medical armamentarium of 25 years ago. The spiralling standard of living has brought with it the fear of exorbitant price. And price is now being considered an alternative to future discovery. The world's pharmaceutical manufacturers which have produced the majority of our so-called wonder drugs, admittedly for the motive of profit as with most other activities in our market economy, are being condemned for extravagance and their motives subject to trial by headline. In fact,

the very substantial discoveries of the industry have been belittled in the United States, (22/) and even in our own House of Commons. 23/

As the industry stands at the dock of public opinion, we might well ask ourselves whether lack of knowledge and misunderstanding will again result in a roadblock to future discovery; whether research will again recede into the fear of the unknown. Dramatic though this may appear on the surface, movements are under way which would seriously undermine research by private enterprise. Regardless of the work of government, the curtailment of free enterprise laboratories will hamper the pace of research and discovery.

We will not reiterate in this submission the pharmaceutical manufacturing industry's contributions to medicine, for these are explained in the attached copy of the representation which we made before the Ontario Government's Select Committee on Drugs, under Appendix D. But at the present time there is no missile gap in pharmaceutical research, and there can be no doubt that thousands of Canadians living today owe their lives to new therapeutic substances discovered or developed by scientists working in the laboratories of pharmaceutical firms.

Granted, compared to a nation the size of the United States, Canada's role in the field of pharmaceutical research is comparatively small. But we are presently a small nation, even though we do have a tremendous potential. As our population grows, and our domestic markets increase, our industry will eventually gain its rightful place in the scheme of international research.

Concrete signs of this future development are now on the horizon. Some of our companies already have extensive research

laboratories in this country, and this has given Canada a good foothold in pure and applied research. And at least one of these commercial laboratories is among the largest research establishments in Canada and is devoted solely to the field of pharmaceuticals.

Other pharmaceutical companies, particularly subsidiaries of foreign research houses, are commencing to build up pharmaceutical research laboratories in their Canadian operations. Still others are contributing experience and finances to our independent researchers and universities.

As evidence of the significance of this assistance, we are attaching to this submission under Appendix E, a list of 158 research studies and fellowships published in the Canadian Medical Association Journal between January 1958 and June 1961, which were supported by pharmaceutical manufacturers. Furthermore, this list does not contain mention of all studies and fellowships supported by pharmaceutical manufacturing during that period. At best it is merely a partial list appearing in one journal.

Clinical investigation in Canada has had a significant growth over the past seven years, particularly in respect to subsidiaries of foreign companies. As you know, this is the final stage of a research project where the new product is studied in humans under controlled supervision after leaving the laboratory and before being placed on the market. As recently as 1954, only a limited amount of clinical research was being done in this country. Since then the amount has mushroomed to the point where today the clinical trials for a new product are usually carried on in Canada simultaneously with the trials being conducted in the country of origin. The contribution of

Canadian medicine in the clinical evaluation of drugs is now widely recognized.

The clinical investigation stage of research and development usually comes under the aegis of a company's medical director. The medical director, in addition to his liaison with the medical profession, devotes a large portion of his time to initiating and supervising various clinical investigations to evaluate potential new drugs. He is also required to check all medical literature and other promotional material before release. His role in the industry covers a wide area, and he must keep himself constantly up-to-date on all new forms of treatment and on the changes taking place in the practice of medicine. Together, these medical directors constitute a specialized group of physicians. They have their own section within C.P.M.A. which, in turn, is affiliated with the Canadian Medical Association.

The following page contains the results of two surveys of the research and development expenditures of our member companies: One covers 22 companies for the years 1958 and 1959 undertaken by C.P.M.A.; the other covers 35 companies for the year 1960, undertaken by Clarkson Gordon & Company of Toronto. For this survey, we asked the companies to break down their research and development expenditures incurred in Canada. In addition, we asked for the share of research and development costs charged to subsidiaries by parent corporations for research undertaken in other countries, on the grounds that this amount of money must be reflected in Canadian prices.

From the results of the Clarkson Gordon survey, you will notice that these 35 firms accounted directly or indirectly for total research

RESEARCH AND DEVELOPMENT EXPENDITURES BY 22 COMPANIES IN 1958 AND 1959 24/

	1959	1958	% gain
Total cost applicable to firms operating in Canada:	$5,324,613	$4,718,770	13%
Spent by foreign control on behalf of Canadian subsidiaries:	2,614,900	2,288,757	14%
Actually spent in Canada:	2,500,165	2,238,185	12%
Research projects underwritten abroad by Canadian firms:	209,548	191,828	9%
Clinical investigation:	362,889	302,288	20%
Research gifts and grants:	327,784	298,358	13%
Capital expenditures on research and development laboratories and equipment in Canadian plants:	2,456,332	1,266,582	94%
Percentage of total cost of all research and development in relation to Canadian net sales:			6.3%

RESEARCH AND DEVELOPMENT EXPENDITURES BY 35 COMPANIES IN 1960 25/

Total cost applicable to firms operating in Canada:	$9,551,000
Spent by foreign control on behalf of Canadian subsidiaries:	6,202,000
Actually spent in Canada:	3,349,000
Clinical investigation:	1,022,000
Research gifts and grants:	414,000
Capital expenditures on research and development laboratories and equipment in Canadian plants:	2,968,000
Percentage of total cost of all research and development in relation to Canadian net sales:	8.3%

expenditures in 1960 of $9,551,000. Of this amount, $3,349,000 was actually spent in Canada, while $6,202,000 was incurred on behalf of Canadian subsidiaries by foreign companies. In addition, capital expenditures on research and development laboratories and equipment in Canadian plants totalled about $3,000,000.

Referring to the survey covering 22 firms for the years 1958 and 1959, it is interesting to note that these companies spent more on pharmaceutical research in Canada in 1958-59 than that expended by either the National Research Council or the Department of National Health and Welfare for extramural medical research, as reported in the green book. And the term medical research in respect to these two government agencies is not limited to pharmaceutical research. Furthermore, the voluntary health agencies interested in specific diseases such as arthritis, cancer and muscular dystrophy, cannot be considered an effective alternative to general pharmaceutical research. A large portion of their funds must necessarily be spent on education, and the expenditures on research by these agencies go towards medical research in its broad application.

It is for these reasons that we question the comment in the green book that "research in Canada appears to be regarded more and more as a responsibility of government and of those private organizations interested in particular diseases." In the field of drug research Canada's pharmaceutical manufacturing industry is presently doing its share of investigation.

If this research continues to grow at the rate of 12-14 per cent per year, the annual expenditures on research and development in Canada by these 35 firms alone will have reached at least

$11,000,000 by 1970. Nor does this take into account the anticipated growth of the domestic market which will make it economically practical for more and more companies to establish research facilities in this country.

We must be realistic in viewing the future of pharmaceutical research in Canada and the role of the Federal Government in this respect. Had the U.S. Government taken over all pharmaceutical research in that country, and closed incentive to private enterprise, it would now be faced with either adding another $200,000,000 annually to its budget or curtailing that nation's current research efforts. 26/ The coffers of government are not bottomless.

It was coincidental that the 1959 research surveys by our Association and the Combines Investigation Branch each based its results on 22 companies, for our survey was published before the Ontario Inquiry in October, 1959, while the green book was not completed until February 1960. Presumably the 22 firms reported by the green book are included among the 27 firms listed on pages 106-107. Our own survey resulted from returns of 28 firms, 22 of which replied to the research chapter of the questionnaire. 27/

Yet of these two lists, only 14 firms appear on both. The green book contains the names of 13 firms which were not in our survey, while our survey contains the names of 14 companies which were not included in the green book survey.

Pro-rating the average of 2.12 per cent of the total sales figure of $94,600,000 mentioned in the green book, produces a total expenditure on research in Canada for these 22 firms of $2,005,520. It will be noticed above that our figure for the same

period and for the same number of companies was $2,500,156. Both are sufficiently close to bear favourable comparison.

However, there is one rather notable discrepancy. The 22 firms mentioned in the green book are reported to account for total sales of $94,600,000 whereas our own annual statistical figure for the same period shows 43 firms with a total sales of human pharmaceuticals of $96,516,511. 28/ Even though some of the firms mentioned in the green book were not covered in our survey, it is doubtful that 21 companies would account for only about $2,000,000 sales.

As the author of the green book will no doubt agree, statistical percentages can be confusing unless the same terms of reference are used in comparisons. For this reason, we venture that this $94,600,000 figure shown in the green book undoubtedly represents total sales of all products manufactured by most of the companies in question and not merely that of human pharmaceuticals. For instance, our survey produced a total sales for 43 firms of $130,755,546, whereas only $96,576,511 of that was in human pharmaceuticals. The balance, $34,239,035, comprised chemicals, proprietary medicines and other products. If this is the case, then the percentage of research expenditures to sales mentioned in the green book is lower than it should be, on the premise that the ratio on research for ethical pharmaceuticals should be limited to sales of ethical pharmaceuticals.

Carrying this approach to its conclusion, we suggest that the green book's percentage of research should be closer to 3.1 per cent of sales rather than 2.1 per cent. This reasoning is based on the fact that our own survey for the same year showed a percentage to sales of 6.3 per cent, and this included research assessments

against Canadian subsidiaries by foreign parent companies. As this assessment dollar-wise represented about half the total research figures of 6.3 per cent, the balance would work out to about 3.1 per cent for actual expenditures in Canada. Again these figures are close enough to warrant accounting comparison.

Comparisons with other industries have been used in respect to profits, so it is natural that we should use them here. The Dominion Bureau of Statistics' publication entitled "Industrial Research-Development Expenditures in Canada, 1959" shows the direct research-development expenditures as percentage of sales for 15 major industries in Canada. All are well below pharmaceutical manufacturing as is shown on the following page.

It will be noticed that our 6.3 per cent figure has been used for pharmaceutical manufacturing, as this includes research done outside Canada on behalf of Canadian subsidiaries. The reason for this is that the DBS survey was based on the same factor, to wit: "In order to ascertain the total cost of research-development, respondents were asked to report not only the cost of their own activities in this field, but also payments made to other companies or organizations both within Canada and outside the country".

If the Dominion Bureau of Statistics uses this as a proper basis for determining research expenditures, then we should feel free to use the same basis, showing the 6.3 per cent figure rather than merely the amount actually expended in Canada. Either way, pharmaceutical manufacturing shows a higher ratio of research to sales than all other major industrial classifications.

It is further significant that this same DBS publication

for the year 1957 (not shown in 1959 issue) indicated the medical research portion of the chemical industry, which would be primarily pharmaceutical manufacturing as having expended $1,340,000 on research in 1957, as compared to other non-manufacturing (sic) which primarily represents "hospitals maintaining research-development establishments and medical foundations" at $1,108,000.

The Canadian pharmaceutical manufacturing industry's research expenditures may be considerably less than those of its U.S. counterpart, but there is no doubt that in relation to other research in Canada, both medical and general, our industry is one of the top contributors.

As our nation grows and the market for pharmaceuticals in Canada expands, domestic pharmaceutical manufacturers will be able to increase their research facilities accordingly, and the nation will depend less and less on other countries for the advancements essential to the health of our people. This dependency will gradually disappear, but only if this industry continues to grow and prosper.

There is still another aspect of Canadian research and that is the scientists who work in our laboratories. The two surveys which we referred to earlier showed the following breakdown of scientific personnel employed by these companies:

	34 firms	22 firms	
Type of Researcher	1960	1959	1958
Ph.D., D.Sc., or M.D.	102	76	74
M.Sc. or Equivalent	28	18	18
B.Sc., Phm.B. or Equivalent	90	60	54
Laboratory Technicians, etc.	142	107	100
Total	362	261	246

Direct Research-Development Expenditures as Percentage of Sales, 1959

	Direct research cost as % of sales
Pharmaceutical manufacturing:	6.3%
Transportation Equipment:	1.90%
Electrical Apparatus and Supplies:	1.81%
Chemical Products (which include pharmaceutical manufacturing):	1.54%
Mining, Quarrying and Oil Wells:	0.99%
Non-ferrous Metal Products:	0.71%
Tobacco and Tobacco Products, Leather Products and Miscellaneous Manufacturing Industries:	0.65%
Textile Products:	1.22%
Non-metallic Mineral Products:	0.78%
Rubber Products:	0.53%
Iron and Steel Products:	0.40%
Paper Products:	0.44%
Products of Petroleum and Coal:	0.3%
Wood Products:	0.23%
Transportation, Storage, Communication and Public Utility Operations:	0.14%
Food and Beverages:	0.12%

NOTE: "Industrial Research-Development Expenditures in Canada, 1959" does not show pharmaceutical manufacturing. The 6.3 per cent figure is based on the C.P.M.A. survey.

These are scientific personnel employed by some of the companies in our industry. As we stated in our representation before the Ontario Government we have in the past been losing many of our scientifically-trained people to other nations, but the incentives at home are commencing to improve. If we do not encourage this conducive climate in relation to our growth, we will discourage scientists, for scientists will not remain in a country which does not offer opportunities for jobs and advancement.

We represent a young industry which is making a marked contribution to the health, economy and scientific well-being of a growing nation. And we ask not for political or economic favours, but merely for an understanding of what our companies have and are accomplishing for the good of Canada.

PRODUCT NAMES

As the green book points out, much confusion exists in the area of product names. Some claim that by eliminating the trade name and using only the generic name phenomenal savings can be realized in price, completely ignoring the fact that economics of business govern price and not merely the name assigned to the product. Others claim that ethical pharmaceutical companies selling under trade names are bitterly opposed to generic names, again ignoring the fact that many of these firms also sell under generic name.

Briefly, a trade mark or trade name identifies both the product and the manufacturer of that product, while a generic name merely identifies the ingredient. Pharmaceutical manufacturers generally sell most of their products under trade names and, as a result of their advertising and performance, these products become known and accepted by the medical profession.

Consequently, manufacturers or importers dealing almost exclusively in generic names, invariably sell their products as a direct result of the demand created by and for the trade named products. For this reason, it is usual practice for a company selling primarily under generic name to pick up only those products which have the greatest sales potential and for which a market has already been created.

Competitively, the company selling under generic name is not in as good a position as the company which sells under its trade name, primarily because most doctors will not readily prescribe products of unknown manufacture. This, of course, could be overcome by using the generic name along with the company name, but this is the same principle as that of using a trade name. Furthermore, to make its name known to the profession, the company selling under generic name would have to advertise, but by so doing it would add to its costs and so lose its primary advantage of price. If all products could be sold under generic name, this would tend to squeeze out the smaller companies and thus curtail competition in the industry.

The green book states, on page 25, that "there appears to exist a concerted campaign to characterize the products of certain firms which offer imported drugs under their generic name as cheap imitations of inferior quality." The word "concerted" means to arrange by mutual agreement. If this statement is intended to apply against the manufacturers we represent, then it is incorrect.

Our Association has not arranged any such campaign. Where statements concerning inferior quality have been made, then we suggest that such statements are founded on sufficient fact to warrant such claim.

The general tenor of our Association's position in respect to generic names may best be summed up in a statement made by Dr. Newell Stewart of the National Pharmaceutical Council before one of our general meetings: "While I know of no responsible person associated with any pharmaceutical company who is critical of generic names for drugs, there is great opposition to the idea of equivalency of all drugs with the same generic name." 29/

The term "generic name" which is a substitute for the term "proper name" or for the term "common name" has only been publicly used in its present context in the past few years. However, the term proper or common name is not new to the industry. It has always been used by pharmaceutical manufacturers in this country.

It is interesting to note that the term generic name does not appear anywhere in the Food and Drug Regulations. The regulations for labelling state that the proper name must appear on the label of a trade name product in type not less than half the size of the type used for the trade name, when the product contains a single drug. However, when the trade name product contains two or more drugs there can be no proper or generic name for such a product. Only one or two exceptions exist. Therefore, a large percentage of trade name products cannot be identified by a proper name, common name or generic name.

On the label of a trade name product containing two or more drugs, the proper or generic name appears only in the tabulation of the formula. Consequently, the pressure to induce doctors to prescribe by generic name or for consumers to demand generic name drugs in their prescriptions is not practical.

The reference in the Food and Drug Regulations to a

"proper name" is where a monograph for the drug has been published in one of the several compendiums, such as the U.S.P., the B.P. or the National Formulary, etc. A list of proper names for various drugs appears in section C01.002 of the Food and Drug Regulations. The reference to a common name means the name by which the drug is commonly known and for which a monograph has not been published.

Apart from the fact that trade names are a basic fundamental of our free enterprise system, the simplicity provided by trade names is sufficient in itself to justify their use. A detailed study of 889 prescriptions by Dean F. N. Hughes and Professor G. C. Walker of the University of Toronto showed that 781 of these prescriptions specified trade names. 30/ Of these 781, 376 or 42.3 per cent were written for products containing more than one medicinal ingredient, while 405 were written for products containing a single medicinal agent. This illustrates our point about the simplicity provided by the use of trade names. Consider the position of the doctors in prescribing these drugs under a non-trade name system:

Regarding the 405 single ingredient products, the doctors would have been required to remember both the generic names of the products, many of which are long and complicated, and the names of the manufacturers.

Concerning the 376 products containing more than one active ingredient, the doctors would have been required to remember each of the ingredients, their generic names, the quantity of each ingredient, and the name of the manufacturer.

We suggest that this would place an intolerable burden on the prescribing doctor and dispensing pharmacist. Furthermore, it

is inconceivable that an industry as important as pharmaceutical manufacturing would be denied the right, which extends to every other segment of industry, to use a trade name for its products.

The philosophy of insisting that all drugs be prescribed by generic name does not mean that all such prescriptions would be filled with non-trade name products. Witness the statement before this Commission by Mr. Walter Maday of the Alberta Pharmaceutical Association:

"Should it be the policy of physicians to prescribe by generic terminology the retail pharmacists of Alberta would not be unhappy. They would wish it known, however, that they do not interpret this to mean that they are required to supply the cheapest. It is a fairly well recgnized axiom that the cheapest is not necessarily the most economical." It is doubtful whether the public of Canada would stand for any measure which demanded that the cheapest preparation be sold without regard for the reputation of the maker.

The average Canadian can well afford the price of today's pharmaceuticals, as has been shown, and he will insist on receiving a product from a company in which his physician has confidence. This product could be either under generic name or trade name, but it is essential that the physician have absolute faith, based on his own personal experience, in the integrity and ability of the company to provide consistently good quality and performance and this is not something which can be ensured by legislation alone. Contrary to the green book's statement in this respect, wholesalers do stock products under generic name, and druggists can "obtain them quickly and easily".

As we stated at the opening of this chapter, many brand

name companies also sell under generic name, products which carry no trade name. A survey of 39 companies which we undertook in August past, showed that 18 of these firms sell more than 400 products under generic name alone. 31/ And these companies are considered prestige firms by the medical profession. If we, as an Association, bitterly attacked generic name suppliers then essentially we would be attacking many of our member companies, which is not likely.

Our sole stand here is that we are unalterably opposed to any system which would prevent the doctor from prescribing for his patients the products in which he has the utmost confidence. If the trade name became obsolete, price alone would become the criterion for Canada's pharmaceutical manufacturing industry, and quality and performance which are of prime significance, would be lost. There would no longer be the guarantee of reliability in the manufacturing of drugs which is demanded by the doctor and is so important to the patient.

As Dr. Stewart stated, there is great opposition to the idea of equivalency of all drugs with the same generic name. The reason for this is that all competitive products of the same chemical composition are not necessarily equivalents. This was borne out by the Hinchcliffe Committee on Cost of Prescribing in its report to the U.K. Ministry of Health: "The term 'equivalent' may be used in two different senses. It may imply identical equivalent, where the identity is susceptible to proof by chemical methods but even with products containing identical therapeutical substances there may be pharmaceutical variations. The term 'equivalent' may also imply a therapeutic equivalent which can only properly be decided by the prescriber." 32/

Any experienced director of quality control knows that chemical analysis alone is not sufficient to tell whether one product is identical in every respect to another. A product can meet chemical analysis for label claim and conform with pharmacopoeia requirements, yet still contain some variation produced in the manufacture which could provide an effect on the patient not expected by the physician.

In the case of the United States Pharmacopoeia, for example, the requirements are essentially minimums, and the standards set by most pharmaceutical manufacturers are generally higher in terms of efficiency.

Here are a few instances of this:

1. Regarding Tetracycline capsules: Studies of the absorption of tetracycline into the blood stream after administration of the capsules, showed that different formulations produced different concentrations of tetracycline in the blood. It has been found that if calcium compounds, like calcium diphosphate, are added as a filler during encapsulation of the tetracycline, it will bind some of the tetracycline and prevent it from being absorbed. This would result in much lower tetracycline blood concentrations.

It has also been found that citric acid will markedly improve the absorption of tetracycline and give much greater concentrations of this drug in the blood. Also, glucosamine may enhance the absorption of tetracycline. The USP does not specify that calcium should not be added to a capsule formula, nor does it specify that substances like citric acid and glucosamine would aid in the absorption of tetracycline. Accordingly, there could be differences in a product quite important to the patient, and yet they would be USP tetracycline capsules.

2. In the preparation of procaine penicillin G suspension, and sterile penicillin dihydrostreptomycin for suspension, each manufacturer has to make his own formulation to meet his definition of a satisfactory product. The USP permits the use of one or more suitable, harmless suspending or dispersing agents and preservatives, but does not state what these should be.

There are a number of such substances, such as carboxymethyl cellulose, polyvinylpyrrolidone, the tweens, lecithen, etc. Depending upon the manufacturer's particular formula, some of these preparations remain suspended for longer periods of time than others. Some may be thicker or thinner suspensions. Others may produce considerable foam when shaken. Still other companies treat the surface of the glass with silicone to prevent the preparations from adhering to the glass surface.

All of these may pass USP requirements, but a physician may prefer one company's product over that of another, because of its ease of suspension, viscosity and other similar factors.

3. Regarding ointments, the USP states: "In official ointments and suppositories the proportions of the substances constituting the base may be varied to maintain a suitable consistency under different climatic conditions provided the proportion of active ingredients is not varied."

It is recognized that variations in the proportions of the ointment base could cause differences in the absorption of active drugs through the skin. Also, some manufacturers in preparing ointments micropulverize the active drug ingredients so that they are extremely smooth and non-gritty. This could be particularly important in the case

of ophthalmic ointments where lack of irritation due to the medicament itself may be a factor in why the doctor would prefer one product over another.

4. Sterile procaine penicillin G with aluminum stearate suspension is made by suspending procaine penicillin G in oil that has been gelled with two per cent aluminum monostearate. There is a definite art in preparing this aluminum monostearate oil gel. If the gel is not prepared properly, upon injection the concentrations of penicillin remaining in the blood may be of a considerably shorter duration than with a properly prepared gel.

Consequently, it was found that one company's product gave penicillin blood concentrations, after the injection of 1.0 ml. containing 300,000 units, for 96 hours. Other preparations tested varied in their prolongation of penicillin blood concentrations from 24 to 72 hours. As the USP does not specify the manner in which the gel should be prepared, there can be important differences between two products although both would pass USP requirements.

A medical practitioner learns by experience the effect of a particular product on his patients. He undoubtedly has prescribed over the years various products of the same designation produced by several different companies and, finally has settled on one which he prefers for a variety of reasons. To deny that doctor this particular product would, in effect, be taking the responsibility for the welfare of his patients out of his hands.

In an article in the Journal of the American Medical Association, by Dr. Gerhard Levy of the University of Buffalo and Dr. Eino Nelson of the University of California Medical Center, it was stated:

> "Formulation of drugs into various dosage forms may modify profoundly the onset, intensity, and duration of physiological response, the correct dosage for the patient, the incidence and intensity of side effects, and the stability of the drugs. These effects are illustrated by examples from the clinical and scientific literature. Because of the modifications discussed, it is clear that in some cases choice of dosage form and manufacturer's brand may be as important as choice of the actual therapeutic agent." 33/

This is further borne out by an article in the Canadian Medical Association Journal concerning problems involved in the physiological availability of the product, Dicumarol, by a research director of the company concerned. In concluding his remarks, Dr. E. Lozinski stated:

> "Different brands of products, although similarly labelled with respect to active ingredient content, may not provide similar physiological responses. A brand name has implications beyond commercialism." 34/

Dr. C. C. Misener of the Department of Veterans Affairs testified before this Commission that, "It is the policy to have newer drugs obtained from less known companies assayed and tested by the Food and Drug Division (sic) . . . Sometimes shipments have to be rejected due to low quality . . . " These facilities are not available to the general practitioner, who, regardless of the differences between so-called equivalents, must rely on his own experience. Furthermore, laboratory testing of the end product is not an absolute guarantee of efficacy and safety. Such testing must be preceded by exacting quality control procedures during the entire manufacturing process.

As you are aware, the Food and Drug Directorate is presently establishing requirements for the manufacture and importation

of drugs, which will tend to strengthen existing regulations. Notwithstanding comments made to the contrary in Winnipeg, these proposed new regulations originated in the Food and Drug Directorate, and our Association as well as other interested groups have been working closely with the Directorate on the countless details involved.

In this connection, we undertook an extensive study of what might be done to strengthen manufacturing requirements in Canada. The results of this study were then submitted to the Directorate. A considerable amount of work has since been done by our Association in this respect, and it is interesting to note that our companies are unanimously in favour of strong and enforceable regulations.

The reason for this is that most ethical pharmaceutical manufacturers now maintain strict control in their manufacturing operations to ensure the efficacy and safety of products and their consistency from batch to batch. This is a form of self-regulation, as there is presently no law requiring such control for pharmaceutical preparations. There can be no doubt that this is in the best public interest, and we believe that every product imported or made in Canada should be produced in conformity with sound manufacturing principles and under proper quality control procedures. Obviously, it would be most difficult for any government body to guarantee every batch of products sold. But the proposed regulations are a move in this direction, and we believe that the government should be congratulated in taking this forward step.

Some lay authorities in this country apparently are under the mistaken impression that these forthcoming regulations will in essence place the government's stamp of approval on every product sold

in Canada. As has been mentioned many times, it is virtually impossible for the government to verify chemical analysis, efficacy, potency and the countless other factors involved, of every batch of drugs marketed in this country. Not only is it impractical from an economic standpoint, but quality control is not something which can be determined from analysis alone. It must be built into the product during manufacture.

The green book comments on the "alleged superiority of drugs sold under brand names over drugs sold under generic names." The superiority of the brand name system is not an allegation but a fact, based as it is on the integrity of the maker. This naturally does not mean that every person who places a trade name on a product provides equal quality, reputation and performance, any more than a government purchase ensures the quality of all generic products sold at retail.

But it stands to reason that a company which is prepared to place a name on its product, and establish a reputation for consistent quality with the medical profession, is going to do its utmost to ensure that the high quality of the product is maintained and is consistent from batch to batch during its lifetime. No large company could retain its share of the market without this product consistency, for it has invariably attained its position by proving to doctors over the years that it has a sound reputation for uniformity. Promotion by itself will never sell a doctor on products in which that doctor has found inconsistencies over the years.

To be completely successful in this industry, a company must first earn the confidence of the medical profession. And there is no short-cut to gaining this confidence.

The green book draws a line between large and small manufacturers and in at least one place infers that there is a comparison between a "small" firm and a so-called "fringe" firm. If the intent is in its derogatory sense, then it is incorrect. Many small firms are reputable and highly respected companies. In another reference to a controversy between Parke Davis and Intra Medical, the green book creates the impression that this was in the brand v. generic area, tied in as it is to that subject in the green book. This probably was not the author's intention, but it would create that impression to an inexperienced person.

Both Parke Davis and Intra Medical sell under trade name and, if anything, this controversy indicates clearly that there is strong competition in this industry.

We do not propose to go into the complexities of quality control in this submission, but if the Commission so desires, we are prepared to answer any questions concerning quality control which you may have.

ADVERTISING AND PROMOTION

As an auxiliary to the medical profession, the pharmaceutical manufacturing industry has four main areas of responsibility:

1. To study and develop through research, new and improved forms of medication, and to discover and improve methods of producing these substances so that they are available in sufficient quantity to meet the needs of the profession.

2. To manufacture under controlled conditions for use by the profession all known medical substances, and to ensure uniformity, safety and therapeutic effectiveness.

3. To distribute these substances to all retail pharmacies and institutions across the country immediately they are available, and maintain supplies.

4. To let the professions know immediately new discoveries and improvements are available, so that they may be included in the practitioner's armamentarium, and to ensure that the physician is kept aware of the availability of these new drugs.

These four stages are interdependent, in that they comprise a chain of continuity which ensures the nation of a constant supply of the latest and most effective medication available. No single stage is sufficient unto itself, without the other three. Nor can one stage be dropped without materially affecting the efficiency of the system, which is one of the finest of its kind in modern society.

This chapter deals with the communication stage, referred to as advertising and promotion. This area of endeavour has been subject to much criticism. Yet it is vitally important to the physician who must in the best interests of his patients keep abreast of the latest progress in pharmaceuticals. It helps to reduce the time lag between discovery of a product and its uses in medical practice.

It has been said that 70 per cent of today's medical practitioners completed their internships at least 10 years ago, when penicillin G, streptomycin and the toxic mercurial diuretics were the newest substances known. Many of the medicaments which these doctors learned about from their courses in materia medica have since become obsolete. The decade has brought with it the psychosomatic drugs, new steroids and new muscle relaxants, to name but a few major advances which have occurred in this brief span of time.

Accordingly, advertising not only promotes the companies' products but it also fills a real need by keeping the doctor informed of current developments in the field of pharmaceuticals. Of the many sources of information available to the profession, surveys indicate that the physician acquires about 95 per cent of his information on new

drugs from detailmen, direct mail and medical journal advertising, in that order of preference.

This is borne out in recent studies conducted by International Surveys Ltd., of Montreal which determined, among other things, where doctors first learned about specific products. As these surveys were confidential to companies subscribing to this service, the names of the products involved have been replaced by their therapeutic classifications, as follows:

DOCTORS FIRST HEARD ABOUT PRODUCT FROM:

CLASS OF PRODUCT	DETAILMEN	DIRECT MAIL	JOURNAL ADS.	MEDICAL PAPERS	OTHER
Antidepressant	69.8%	22.6%	--	1.9%	5.7%
Antibiotic	71.4%	14.3%	9.5%	2.4%	2.4%
Antihistamine	66.6%	16.6%	12.5%	--	4.3%
Diuretic	67.3%	20.4%	10.2%	--	2.1%

It is obvious that detailmen and direct mail are the two greatest single sources of information, immediately followed by journal advertising. This is not a case of determining which media the doctor prefers, but rather the one that provides him with the earliest information, for this is the factor which determines the efficiency of any dissemination of knowledge. Many of us complain about television commercials, but we still realize that these commercials make our favourite programs available. They are used because they perform a useful selling function. The same applies to pharmaceutical information and advertising. Many complain about direct mail, for example, yet it serves a basic need for product information and as indicated is used by the profession for this purpose.

This triumvirate of pharmaceutical communications comprises within itself a unique method of ensuring that the doctor

learns of a new discovery, and keeping him aware that the discovery is available. Generally, these three sources of information complement each other. A doctor is an extremely busy man. At given periods, he may not have the time to see a detailman, read a direct mail piece, or study his favourite medical journal. But as these three sources appear before him at different times, the chances are that he will at least learn of the new product from one of the sources. Which one, cannot be determined in advance, particularly when you are attempting to reach thousands of doctors as soon as possible.

For this reason, many companies use all three means simultaneously with the hope that each doctor will at least learn of the new product from one source. This, however, is by no means the rule. Some companies do no direct mail advertising whatever on the grounds that detailmen are the best means of providing complete information to the doctor, and the fact that a large percentage of direct mail is discarded.

Other companies believe that direct mail is an efficient yet economical method of advising the doctor of the product. These firms point out that while a good percentage of direct mail may be discarded it is still the least expensive means of communication, costing as it does but a few cents per doctor. This variance in the use of direct mail was shown in a survey of mailings by 33 companies over an eight-month period from January 1, 1960 to August 31, 1960:

Total No. of Mailings over 8 Months	No. of Companies in each Category
0 to 4 mailings	7 firms
7 to 12 mailings	7 firms
15 to 26 mailings	6 firms
34 to 48 mailings	9 firms
83 to 131 mailings	4 firms

While the average per company was 27 pieces for the eight-month period, the average is not a sound figure in this case. It will be noticed that four firms sent out considerably more direct mail pieces during this period than all the other 29 companies combined. Yet it is conceivable that the advertising costs of these four firms may have been lower than the others in view of the minimal cost of direct mail itself.

Furthermore, this does not mean that each of these mailings went to every doctor in Canada during the eight-month period. Many of them were limited to specialists, such as anaesthetists or urologists. For example, a company may have two new products: a pediatric substance and a psychopharmacological preparation. Information on both products would not normally be sent to both pediatricians and psychiatrists.

In addition, not all direct mail is product advertising. A good percentage is non-promotional in nature and we wish to leave with the Commission a sampling of this type of literature for later study.

Generally, direct mail fills a need not met by detailmen or medical journal advertisements. Most journals are issued monthly and, while their closing dates for advertising copy are more than reasonable, there is a time lag involved. Even the Canadian Medical Association Journal which is published weekly has a closing date 28 days prior to publication. It often takes detailmen introducing new products several months before they are able to visit all physicians in their territories.

Direct mail is the fastest means available for sending

out product information and it is most economical, particularly when used in large quantities.

Medical journal advertising is also another important source of information for the doctor, yet it has been criticized as being flamboyant, misleading, and with no mention of contraindications. It is a known fact that most Canadian journals carefully screen the copy for advertisements prior to insertion. It is also common practice for all major companies to have their copy reviewed by physicians before is is sent to the journals. In some cases, the copy is written by doctors, or, in the case of a new discovery, by a medical advertising specialist in collaboration with the company's director of research.

Visually, the so-called flamboyant pictorial style used in journal advertisements is not as unusual as it may appear to the uneducated eye. An advertisement to gain readership must be more than a box of black type. It must carry a pleasant layout of copy, and to a higher intellect such as a professional man this layout must be in extremely good taste.

Secondly, it is usual practice to include in the advertisement a picture or design to improve the type layout. In journal advertising, the picture used invariably is intended to depict in some form the medical problem involved.

As a general condemnation of advertising copy that has been submitted to this Commission, we have attached to this submission a copy of the August issue of Applied Therapeutics, and we would ask you to review with us some of the advertisements in this journal, as follows:

The first ad on the inside front cover shows a man suffering anxiety and tension. We draw to your attention the heading; the product is for this very purpose. You will also notice that this ad indicates to the physician that the product is available only on prescription.

The next ad contains a semi-caricature of an obese individual. As might be expected, the product is for weight control. Here, there is a specific notation regarding contraindications with a suggestion for an alternative product. On the following page appears a photograph of grass or a straw-like substance which most certainly is indicative of an anti-allergenic product. This ad, as well as others in this journal, advises the physician that there is a more extensive medical brochure available on request.

Turning the page over, we find a few medical instruments to brighten a claim for an anti-bacterial infection substance. Here, it states that tests in nearly 11,000 patients indicate "no cases of serious side-effects or toxicity were reported." Again turning the page, we find an experimental plate as the only bright spot in this advertisement, and we suggest that this straight-laced layout is the antithesis of flamboyance.

On page 586, we find an ad with no central illustration whatever. Note the sentence: "Literature and samples gladly supplied on request." The facing page contains what might be termed a special insert on a heavier stock paper. Aesthetically, the illustration is in extremely good taste, indicating as it does an artistic conception of depression. The copy on the other side of this insert spells out in detail the side effects involved and how they may be controlled, and

specifically warns against the product being used in certain cases.

Two pages over, on 592, there is a double page ultra-conservative layout, advertising the introduction of a new tranquilizer. Here, you will notice that this suggests that the doctor obtain complete information on "indications, dosage, precautions, and contraindications," from either the company's detailman or medical director. Both are at the doctor's service for complete information.

The following page shows an ad for an antibiotic. Rather than flamboyant, this picture is somewhat stereotyped and old-fashioned when compared to the usual lay magazine advertising, showing as it does the young patient, the worried mother and the doctor. But it is interesting enough to cause some doctors to pause for a moment when looking through the journal.

Again, on page 596, appears an ad for a cholesteropenic agent; a new product being released after eight years of developmental work at both the basic and clinical research levels. You will note that this ad offers the doctor a 20-page explanatory brochure for his further consideration. The next ad would be particularly appealing to a trout fisherman and, while this Jock Scott fly may seem irrelevant, it is certainly not so to the angler who is susceptible to poison ivy or eczematoid dermatitis.

The following page is largely taken up by a photograph of turbulent water, advertising an established product of one of the most conservative houses in the industry, and one which is highly respected for its integrity. This example is unusual in that the copy is designed to tie in with the illustration instead of the other way around, such as the ad on the following page which shows an emblematic rigidity to denote the Parkinsonian patient.

Turning over to page 619, what could more realistically carry the connotation of a prenatal supplement than this caricature of a stork. And we doubt whether this long-billed individual would carry a psychological depth sufficient to brain-wash any obstetrician.

This explanation merely covers the first-half of this particular journal, and we will not belabour you with the remainder which are of the same pattern. But these advertisements are typical of this field of information. This journal is published by a commercial house as compared with a medical society organ. But regardless of the implication left with this Commission by one witness, there is no difference whatever between the advertising which appears in this publication and that of the CMAJ, for example. Although commercial in nature, this journal has a high professional standing. Not only are its national board and consultants drawn from among some of the senior medical authorities in Canada, but its editorial board of independent physicians reviews the advertising which appears in the book.

Incidentally, while you have a copy of this excellent journal, you might be interested in reading the editorial which appears on page 595, referring to this Commission, particularly the last paragraph which reads in part as follows:

> "We believe that well-conducted hearings of this kind are a useful procedure in any modern democratic society. We do not believe that uncontrolled statements made by persons who suffer from a high index of irritability are in the least helpful. For example we hear or read dramatic statements about the promotion methods of pharmaceutical houses. When one stops to reflect, criticism of this kind strikes very deep indeed into the structure of our Canadian community. Do we want our whole health system to abandon all individual and competitive activity? If we want drug manufacturers to stop competing with each other for attention and sales then we must surely want state control of the industry . . . or so some of the statements made by members of our

profession would lead us to believe! It seems most unlikely that this would be a generally acceptable view."

Furthermore, lest there be any mistake about the medical profession's views concerning pharmaceutical advertising, we submit for your consideration the following editorial which appeared in the Canadian Medical Association Journal on March 25, 1961:

> "Berating the pharmaceutical manufacturers has become a highly popular pasttime. Some of the criticism levelled at the industry seems valid and constructive; a considerable proportion is unfounded and misleading. The pharmaceutical industry's contribution to the conquest of disease, the betterment of health and the remarkable advances in every facet of science and practice of medecine, beyond doubt, has been a major one. In this endeavour the pharmaceutical manufacturer has been and should continue to be a close and trusted ally of the physician. His role in this partnership involves the development, testing and perfection of a rapidly increasing range of pharmaceuticals. Those that meet the high standards demanded of them are launched in a highly competitive market where they must be sold to survive.
>
> "A good product will achieve satisfactory sales if it is therapeutically beneficial without deleterious effects, but it will not become widely used unless it is widely known. This, perforce, involves advertising and since ethical pharmaceuticals are largely or entirely dispensed on the advice of physicians the advertising must logically be directed to physicians. The quality of such advertising may be good, or it may be bad. Since the physician is its major target, it is reasonable that he should voice his opinions concerning those features of pharmaceutical advertising that he considers detrimental. In Canada he has done this rather bluntly, through the proper channel, his professional organization.
>
> "It also seems logical and obvious that the pharmaceutical manufacturer would be interested in the reactions of the target of his advertising. By no means does this deny the value of sound, reliable advertising of ethical pharmaceutical products, which, on the contrary, has become more important than ever before. The concern of the medical profession emphasizes its recognition of this fact. Pharmaceutical advertising has had and will continue to have considerable educational influence on the practising physician. It behooves the medical profession to work in harmony and mutual understanding with the pharmaceutical industry to raise

the standards of this, as well as other aspects of graduate medical education."

The editorial refers to the fact that the Canadian Medical Association advised us of some features of advertising which it considers detrimental. This was immediately brought to the attention of member companies.

As was mentioned in the CMAJ, a broad and generalized criticism against pharmaceutical advertising is not valid. There is very definite need for this system of communication. It is essential to the dissemination of pharmaceutical information and it maintains the competitive nature of the industry. Companies do not spend money unnecessarily, and if there was a more efficient and effective means of reaching the doctor other than through detailmen, direct mail and journal advertising, the industry would have found it by now.

Promotion in this industry is costly in relation to lay advertising, because of the calibre of the information required and the technical nature of the data involved. Pharmaceutical literature must be carefully prepared, screened by medical men, and presented in a manner that is quickly and clearly understood by the doctor. In addition to the advantages inherent in the product, the literature must also indicate the nature and action of the product, the administration and recommended dosage, and the contraindications, toxicity and precautions involved. By the very nature of these technicalities, the same dollars used in advertising pharmaceuticals will not bring back an equivalent ratio of readership or impact as does lay advertising.

The educational requirements for a detailman are probably higher than that for salesmen in most other fields, primarily because

it is essential that he have a higher education and training in order to provide the answers required by physicians and pharmacists. The large majority of detailmen have university degrees. There is a definite shortage of graduate pharmacists for detailing. While a company may prefer pharmacists for this role, they are not always available. Consequently, the company may have to take someone with a non-pharmaceutical background.

Doctors will not generally prescribe new products solely on the recommendation of the manufacturer. They require complete information in order to evaluate the product's use in practice. If the doctor knows from experience the company concerned has a reputation for reliability in introducing new substances, then he will undoubtedly ask the company's local representative for the required background information. In this manner, the detailman serves as an important contact between the practitioner and the manufacturer, and it is his primary function to acquaint the doctor with the limitations as well as the capabilities of his company's products.

Criticisms have been levelled before this Commission with the connotation that companies and their detailmen attempt to hide or minimize contraindications. This is incorrect, as will be shown in this sampling of literature containing specific references to contraindications, which we wish to leave with the Commission for further study.

As might be expected, all detailmen are not perfect. Their abilities in detailing depend upon their individual capabilities, as it is in any field of endeavour. But it is safe to say that the great majority are well-trained, intelligent individuals who provide a

tangible service to the medical profession. This is indicated by the fact that surveys show the doctor considers the detailman to be his front line of information.

The charts on pages 108-110 of the green book indicate that the cost of detailmen averages out to less than 15 per cent of the sales dollar. The Clarkson Gordon & Co. survey indicated 14.1 per cent for 40 companies. Using this figure as an average, you would save not more than 9 per cent of the sales dollar by eliminating the practice of detailing. The reason for this is that most detailmen spend only part of their time in calling on doctors. The other part is spent in visiting pharmacies and hospitals, general servicing for the company, serving as an on-the-spot point of contact for clinical investigators, and other miscellaneous duties which are essential to any national company. This was borne out by the survey conducted by Clarkson Gordon & Co., which showed that detailmen spend a weighted average of 36 per cent of their time on duties other than detailing doctors.

The question is whether this saving of about 9 cents on the manufacturer's sales dollar, would be worth the undoubtedly adverse result which would occur by depriving the medical profession of its foremost source of product information.

Sampling is another practice followed by the industry when introducing products to physicians. The objective is to give these to doctors so that they can evaluate the drug's usefulness. These samples are often given to patients as "starter doses" to be used until the patient can have a prescription filled. A number of physicians use samples for their indigent patients, and some companies actively support this practice.

The tables on pages 108-110 of the green book show a considerable variation in the percentages of sampling costs to sales. We are reasonably certain that the higher percentages reflect more costly products such as the antibiotics. And these product samples are the very ones which the doctor will keep in his bag for night and emergency calls. Doctors do use samples, and it would hardly be practical to expect the physician to buy these products himself.

A statement was made before this Commission in Calgary by a newspaperman about a doctor who receives "about $2,500 worth of samples from drug companies each year." This figure is too high by at least $2,000.

We asked our companies for the average cost per doctor of all samples distributed during the year 1960. Thirty-nine firms reported a total of $285.17 for an average of $7.31 per company over the 12-month period. 35/ These are all major companies in the industry, and it is doubtful that the remaining firms would produce another total of $214.83, which means that the total cost per doctor sampled in 1960 was much less than $500.

Nor does this mean that all doctors in Canada received $285.17 worth of samples from these 39 companies. Many of these samples were restricted to specialists, while others were distributed only on request to a limited number of practitioners. Consequently, the average for all doctors in Canada would be considerably lower.

The green book quotes on page 111 an excerpt from Harper's Magazine referring to the "lavish" gifts to doctors by pharmaceutical firms in the United States. To determine the extent of this practice in Canada, we polled the same 39 companies for

information on their practices in this respect during 1960.

Of these 39 companies only one distributed a gift to all doctors in 1960. Eighteen firms gave no gifts whatever during the year. The remaining 20 companies reported as follows: Nine limited distribution to graduating medical students and interns, 10 gave gifts on a limited basis to certain practicing physicians, while one gave a pencil and map to delegates attending the British Medical Association convention in the U.K.

In all, the average cost per unit of these gifts was $1.29. Gifts to practicing physicians ranged from calendars and pocket diaries to pencil holders and ball point pens, at an average cost per unit of .82c each. Graduating medical students and interns were the major recipients, receiving introductory product kits, thermometers, diagnostic lights, business cards, etc., for an average per unit cost of $2.19 for the year 1960.

It is recognized that a comparatively small percentage of firms use this type of gift in Canada, and it is obvious from the per unit costs involved that they are by no means "lavish". Incidentally, it is known that promotional practices of this nature are more prevalent in the United States, although it is doubtful whether the claims being made about that industry's operations are any more factual than the ones being directed against us in Canada.

The company mentioned in the green book as having provided plant tours of its U.S. company for graduating medical students is not a typical undertaking by companies in Canada. However, some of our companies do arrange plant tours of their own Canadian facilities from time to time.

This has been criticized as further "brain washing" of doctors. But if pharmaceutical manufacturing is the profession's major supplier, then it stands to reason that physicians should have a first-hand knowledge of how drugs are produced and under what conditions. We wish that more of our companies would use plant tours for this purpose, if for nothing but to dispel the impression being created that pharmaceutical manufacturing is nothing but a few tabletting machines in a small room.

A large plant is a fascinating operation, particularly to someone who is scientifically inclined and, as was stated before the Ontario Inquiry, if every Canadian could tour a well-regulated pharmaceutical plant there would no longer be the misconceptions concerning our industry which have become prevalent in recent years.

Such a tour is essential to a complete understanding of our industry and we extend to the members of this Commission a cordial invitation to visit a few plants in Montreal, which is the nearest major centre to Ottawa. We will be pleased to make the necessary arrangements at your convenience.

Before concluding this chapter on advertising, we wish to comment briefly on a couple of statements made before this Commission by Dr. J. P. Gemmell in Winnipeg.

This witness stated that physicians in the United States receive about 4,500 pieces of direct mail per year and that the amount in Canada is not too "dissimilar". We do not know whether the U.S. figure is authentic, but we do have evidence which shows conclusively that the amount in Canada is less than half that figure.

According to the Medical Mailer for March, 1961, produced by Canadian Mailings Ltd., of Toronto: "The English speaking

doctor (in Canada) received a total of 2,147 pieces of mail advertising during the year 1960." Nor was all of this literature from pharmaceutical houses. The same reference indicates that 18 per cent of this literature was from suppliers of books, journals and equipment, plus general solicitations. Deducting this 18 per cent from the total mailings received by a doctor in the course of a year means that he actually received 1,761 pieces of literature from pharmaceutical houses, which most certainly is a far cry from 4,500.

By way of explanation, it is usual to differentiate between English and French language physicians when discussing advertising literature. As Canadian companies must print literature in both English and French, the cost is naturally much higher proportionately than it is in the U.S., the U.K. or France, where single languages prevail.

It was further uttered before this Commission that the majority of statements made in drug advertising are ambiguous, misleading and with no reference to toxicity. Outside the realm of opinion, if any credence is being given to this particular testimony by the Commission, then we offer this suggestion: That this Commission ask two or three qualified, knowledgeable and completely disinterested medical practitioners to study all promotional literature issued by our companies during the past year, and correlate this information, showing where the copy would be ambiguous to a normally knowledgeable practitioner, deliberately misleading in claims, and containing no reference to contraindiction or toxicity where such would be normally required by an experienced practitioner. If we are to be indicted, then we would prefer to be indicted by fact and not superficial claim.

Furthermore, it was inferred "that in 95% of cases absolutely no information is available on the cost of the drug to the patient." Dr. Nathan Shecter said in Ottawa before this Commission that detailmen will often quote the price. Any detailman will tell you that one of the questions asked by a doctor on the introduction of a new product, is how much does that product cost. Price is not generally included in medical literature, for the simple reason that this literature goes to doctors from coast to coast. To do this, the mauufacturer would have to use his suggested list price which might not be the final price in all areas depending upon differences in prescription fees, the variances in the retailers' overhead in different areas, and similar factors. However, the detailman is quite prepared to discuss the price of his products with the doctor at any time.

It would be possible for us to give our views on every statement made before this Commission during its hearings, but we have merely attempted to select the more pertinent points which we believe are of interest to the Commission. The Commission's major task, of course, will be in the eventual sifting of all the evidence submitted. If at that time specific questions concerning advertising and promotion arise, we will be pleased to submit a supplementary brief, or provide the answers via mail.

PATENTS

The green book deals extensively with the subject of patents, and their so-called monopolistic effect on prices. Broadly speaking, the term "monopoly" in respect to business has gained a notorious connotation. But this is not so when it is used in legal

references to patents. The Patent Act is specifically designed to create monopolistic situations, in that it gives by law a monopoly to the creator of a new product. In most fields, this monopoly is for 17 years. But in the field of pharmaceuticals, this 17-year legal protection has been virtually eliminated by the compulsory licensing provision.

If anything, Canada's patent laws have been specifically designed to prevent a pharmaceutical manufacturer from attaining the same benefits from his research endeavours as do companies in other industries. There is, in effect, a discrimination against medical research compared to other forms of research, which is particularly significant in view of the important role of product development within the industry. This discrimination is based on the assumption that a curtailment of patents rights in medical research is in the best public interest.

It has been suggested, albeit not in the green book, that Canada should do away completely with patents to promote the greater importation of medication from abroad. If this were done in the United States as well, there is no doubt that North America would, in essence, be trading price for future discovery. Consequently, there must be at least a modicum of incentive in the law, for both wholly-owned Canadian manufacturers and subsidiaries of foreign corporations, to further the interests of research and its important bearing on future discovery.

Recognizing this principle and the fact that it is also important to encourage manufacturing in Canada, the government has instituted the complusory licensing provision which serves as a compromise between complete patent protection and no patent protection.

With this background, the green book states that prices of certain drugs are affected by the control exercised through patents, and that the compulsory licensing provision has been ineffectual to combat this situation "and the clear intent of the Act has been frustrated." This conclusion appears on page 257, directly under the paragraph which states in part that "certain conditions have given rise to a great deal of controversy, and judgements about them will necessarily involve opinion".

We suggest that the conclusions concerning patents are based on opinion and not fact. Furthermore, it is significant that of all the representations concerning patents made to-date before this Commission, only one person, the Commissioner of Patents, was qualified to speak on the subject. The remainder largely used the wording of the green book as their sources of information.

Firstly, in respect to prices, the Commissioner of Patents apparently does not agree that patents have a major bearing on prices. In his testimony, Mr. J.W.T. Michel stated that the patent system, if it is a factor in the price of drugs, "it certainly is not the main factor".

It is an economic fact that any company introducing a drug to the market must base its price on those of other products already on the market which compete with it in the therapeutic class concerned. There is virtually no specialty drug on the market today whose therapeutic effect cannot be approximated by some other drug. Regardless of how strong the patent on a new drug, it does not by any stretch of the imagination give that company a free hand to inflate price beyond reason. If that were done, there is no doubt that

detailmen representing competitors' products would bring this point to the attention of the medical profession.

If the process involved in making the product is too costly in relation to that of its competitors, then the company must find a more economical means to bring down costs so that the end price will not be too far out of line. This factor can mean the difference between a large-volume or low-volume product, regardless of the patent.

The green book further submits the opinion that U.S. patent law determines the situation in Canada, and because U.S. firms are so active in Canada their products are the best known and hence the most widely used. We doubt whether non-U.S. companies would agree with this statement.

What is apparent, however, is that the United States "only gets 15 per cent of foreign (patent) applications that come through," according to the Commissioner of Patents. 36/ This would indicate that if subsidiaries of U.S. companies have a proportionately greater share of this market, it is not because of their patent position. It is more likely that the 85 per cent of non-U.S. patents would exert a greater influence on the Canadian market.

From an arms length viewpoint, there are two criticisms of our industry which cannot be reconciled. One is that patents result in a limitation on the number of products placed on the market. The other is that the industry is placing too many products on the market. In one case we are being condemned for preventing others from entering the market with similar competing products while, on the other hand, it is being stated that there are now too many competing products being introduced.

Obviously, both assumptions cannot be correct, and this point is offered as further evidence that pharmaceutical manufacturing in Canada has been unjustly criticized by uninformed opinion rather than substantiated fact. We agree that there is a large number of products on the market in any therapeutic class, but this gives the medical practitioner a choice based on a competitive factor which is most certainly in the best public interest.

There has been some regret expressed before this Commission that not enough companies are applying for compulsory licensing through the Commissioner of Patents. However, the number of applications approved at Ottawa alone cannot be used as satisfactory evidence that the compulsory licensing provision is not working in this country.

Section 41 (3) is working according to the intent and expectations of its legislators. As was pointed out by the Royal Commission on Patents in its 1960 report, "It is generally considered that the mere existence of such provisions leads to voluntary licensing which otherwise would not take place." 37/ In order to bear out this point, we surveyed our member companies to determine the number of licenses which have been granted voluntarily. 38/

The 39 companies which replied to this survey reported they had voluntarily licensed 17 products to 32 competitors within the past six years. The breakdown is as follows:

TYPE OF PRODUCT	DATE GRANTED	NO. COMPANIES VOL. LICENSED
Antihistaminic	1960	1
Local Anaesthetic	1955	8
Ataractic	-	2
Antibiotic Fungicide	1960	3
Synthetic Antimicrobial	1959	1
Oral Antidiabetic	1957	1
Hormone Substance	1954	2
Antihypertensive Tranquilizer	1956	1
Antiseptic	1954	1
Antibiotic	1957	2
Sali-Diuretic & Antihypertensive	1959	1
Cortico-Steroid	1954	1
Injectable	1956	1
"Various"	1957	1
Enema	1959	1
Enema	1959	1
Sulfa-Streptomycin Comb.	1956-59	4

Some of these 39 companies refused to divulge this information on the grounds that it is confidential. One major company stated, "we do not own any patents". Others said that they have taken voluntary licenses from competitors, but have not granted licenses themselves. One of these, a wholly-owned Canadian firm, reported receiving eight voluntary licenses from eight different companies during 1955-60, six of which are not included in the above list.

From the owner's standpoint, it is not always worth the expense involved to contest an application for a compulsory licence patent at Ottawa. The applicant usually applies to the owner first and where the applicant is manufacturing in Canada and has the facilities to make the product, the owner will often attempt to get the best deal possible from the applicant without resorting to legal action. This is the rule rather than the exception. The results of a voluntary license are not generally known at Ottawa for, as Mr. Michel has pointed out, it is not essential that a voluntary license be registered with the Patent Office.

It has been held, and rightly so, that a compulsory license should not be granted to an importer. If this were done, there would be no incentive whatever to establishing manufacturing facilities in this country. Yet a number of importers are actually bringing into this country patented products for which they hold no licenses, in contravention of the Patent Act, and in some cases have been actually selling these products to Federal Government purchasing departments.

From the applicant's standpoint, it is often the economics of the situation which determine whether a license is interesting. For example, it would not be profitable for a company to demand a license for a low-volume product on which the owner is breaking even or operating at a loss. Nor would it be practical for a company to call for a license on a biological when it does not have the facilities with which to make biologicals.

By the same token, a company is not going to demand a license for a product where it already has a competing product in the same therapeutic class. These are but a few of the reasons why licenses are not always requested, and it is incorrect to state that our licensing provision is not working because competitors are not demanding compulsory licenses from each other in profusion.

There are a great number of non-U.S. firms in this industry and if they felt it economically desirable to demand either a compulsory or voluntary license there is nothing to prevent them from doing so. And as we indicated earlier, this is being done continually.

The argument that it takes too long to obtain a

compulsory license to make it worthwhile to the applicant, is relative. Mr. Michel has stated that an application from a competent company and patent agent can be disposed of within a year. That in itself is a short time in respect to the years often required by the owner to produce the process for the original product. It often takes that long to prepare the new drug submission alone, which the originator must submit to the Food and Drug Directorate.

Finally, it would be to the decided advantage of importers to do away with patents on pharmaceuticals in Canada. For one thing, it might conceivably save them the expenses of contesting possible future patent infringement cases. But this would not be in the best interests of Canada or its people. A strong domestic manufacturing industry is vital to the future of our nation, both as a means of retaining national productivity and employment, and as a bulwark for the future medical needs of Canadians.

In the words of Mr. J.W.T. Michel, Commissioner of Patents for Canada:

"I am wondering if too drastic a treatment of the patent system would not harm the modest, but bona fide, efforts of those doing research in Canada more than the... prices of drugs which might be attributed to the patent system. After all, our pharmaceutical manufacturing industry is still quite small, but so were many of our industries not so many years ago."

CONCLUSION

As Dr. Brian Dixon points out in Appendix C, pharmaceutical manufacturing in Canada is a highly competitive industry, and this "competitive activity is generally directed in a

manner which is socially desirable." For the reasons outlined in this representation, any interference with the industry's present methods of marketing pharmaceuticals could have an adverse effect on competition in that it would curtail the competitive activities of the large companies and retard continued growth of the small companies.

It is obvious that no monopoly exists in Canada's pharmaceutical manufacturing industry, for monopoly is resistant to change and change has long been an inherent attribute of this industry. The so-called monopoly through patents is questionable, in that the complusory licensing provision of the Patent Act has virtually eliminated the right normally given to inventors in other fields of endeavour. And, as we have indicated, the compulsory licensing provision is working according to the intent of its legislators.

Pharmaceutical manufacturing operates much the same as other industries in our competitive free enterprise economy. The breakdown of this industry's sales dollar is not much different from the national average for all manufacturing industries. In addition, the majority of drugs sold in Canada are made here, although most raw materials are imported.

Profits are not out of line with the average for all manufacturing in Canada, and prices to retailers compare favourably with those in most other high economy countries. The average Canadian can well afford to purchase pharmaceuticals, for retail prices are within the average worker's purchasing ability. The problem of drug purchases by the small percentage of social or economic indigents in this country is a matter of welfare rather than prices.

Whether elimination of the 11 per cent sales tax is

necessary in light of the reasonableness of price is, naturally, a matter for the government to determine. However, it is evident that considerably more savings can be realized by eliminating the sales tax than by curtailing any other single segment of the present drug economy. Elimination of this tax would result in savings of millions of dollars annually to the consumer of drugs.

Much unfounded criticism has been levelled at this industry in recent years, and this resulted in demands for an investigation of our industry. The Federal Government has now met these demands through the facilities of this Commission.

It is understood that the green book is merely a compilation of material to form the basis for a study of the industry. Witnesses were expected to submit further evidence in support of or contrary to this compilation of material. Significantly, many of the witnesses who have appeared before this Commission to-date have used the green book as their sole source of evidence.

Aside from the expert witnesses, the majority of whose testimony has not been unfavourable to our industry, little evidence has been introduced to bear out the misconceptions about pharmaceutical manufacturing which have become prevalent in recent years. In fact, most of the gross exaggerations submitted by witnesses before this Commission have not been founded on fact or supporting evidence.

From the small number of witnesses which have appeared before this national inquiry, it is evident that there is insufficient evidence for the derogatory claims which have been placed on our collective doorstep. From our standpoint, this was not unexpected, for our industry has indeed been operating in the best public interest.

It is our hope that this public inquiry will help to clear up many of the misunderstandings concerning pharmaceutical manufacturing in Canada. The answer will, of course, be found in the final report of this Commission. Consequently, we have but one request: That the final report of this Commission include information favourable to our industry which is warranted by the evidence submitted.

This request is not as unusual as it may appear on the surface. The publication of the green book and subsequent statements made by certain witnesses before this Commission have resulted in considerable derogatory publicity in the lay press. While much of this was not founded on fact, it has nevertheless become public record. If the material so publicized is found by this Commission to be incorrect, then in all fairness the public record should be corrected. And this can only be done in the Commission's final report.

In conclusion, we wish to thank you for the privilege of presenting this submission to the Restrictive Trade Practices Commission, and are at your disposal to answer any questions you may have concerning the contents of this document.

Respectfully submitted,

Stanley Nesbitt Conder,
General Manager,
Canadian Pharmaceutical
Manufacturers Association.

REFERENCES

1. Globe & Mail, Toronto, June 7, 1945.
2. Pharmaceutical Manufacturers Association, Washington, D.C.
3. Drug Store Audit, June, 1961. International Surveys Ltd., Montreal.
4. C.P.M.A. Survey #2, 1960.
5. Clarkson Gordon & Co., survey #3, 1961.
6. The Financial Post, August 13, 1960.
7. C.P.M.A. Survey #5, 1961.
8. C.P.M.A. Survey #4, 1961.
9. C.P.M.A. Survey #4, 1961.
10. C.P.M.A. Survey #4, 1961.
11. Clarkson Gordon & Co., Survey #3, 1961.
12. Henry Glover & Co., Survey #1, 1961.
13. Clarkson Gordon & Co., Survey #3, 1961.
14. Fuller, H. J.: Retail Costs, Prices and Profits. Canadian Pharmaceutical Journal, September, 1960.
15. Prices & Price Indexes, July, 1961. Dominion Bureau of Statistics, Ottawa.
16. International Labour Office, Geneva, 1959.
17. The Problem of Rising Prices, May, 1961. Organization for European Economic Co-operation, Paris.
18. Prices & Price Indexes, July, 1961. Dominion Bureau of Statistics, Ottawa.
19. Batten, H. M.: House of Commons Debates, February 16, 1961.
20. Statistical Supplement, International Labour Review, July-August, 1961.
21. C.P.M.A. Survey of 14 companies.
22. Kefauver Subcommittee hearings, Washington, 1960-61.
23. Howard, F.: House of Commons Debates, June 22, 1960.

24. C.P.M.A. Survey #2, 1960.

25. Clarkson Gordon & Co., Survey #3, 1961.

26. PMA Report to Committee of Consultants on Federal Medicinal Research, U.S. Senate Appropriations Committee, Washington.

27. C.P.M.A. Survey #2, 1960.

28. C.P.M.A. Annual Statistical Survey for the Year 1959. See Appendix D.

29. Stewart, Newell: C.P.M.A. 1961 Spring General Meeting, Ste. Adele-en-haut, P.Q.

30. Hughes, F. N. and Walker, G. C.: "A Prescription Drug Survey", Canadian Pharmaceutical Journal, May, 1961.

31. C.P.M.A. Survey #4, 1961.

32. U.K. Committee on Cost of Prescribing: Report to Ministry of Health, 1959.

33. Levy, G. and Nelson, E.: Pharmaceutical Formulation and Therapeutic Efficacy, Journal of the American Medical Association, September 9, 1961.

34. Lozinski, E.: Physiological Availability of Dicumarol, Canadian Medical Association Journal, July 23, 1960.

35. C.P.M.A. Survey #4, 1961.

36. Michel, J. W. T., Commissioner of Patents: Restrictive Trade Practices Commission, July 5, 1961.

37. Report on Patents of Invention, Royal Commission on Patents, Copyright and Industrial Designs, 1960.

38. C.P.M.A. Survey #4, 1961.

APPENDIX A

THE CANADIAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION INCORPORATED

The Canadian Pharmaceutical Manufacturers Association was founded in 1914, and was incorporated under the Dominion Companies' Act in 1959. It represents 56 companies engaged in manufacturing and distributing ethical pharmaceutical preparations in Canada.

Membership in the Association is by company, and the categories comprise Full, Associate and Affiliate Member. Full membership consists of companies which manufacture and distribute under their own names in Canada. Associate membership consists of companies which do not as yet manufacture in Canada, but which are subsidiaries of recognized and reputable corporations. When we introduced this system of membership in 1955, there were several companies in the Association which might be considered suppliers to the industry. These companies would not be eligible today, but we permitted them to retain membership in view of their many years of active participation in Association affairs. These firms come under the Affiliate category.

Quality Control

The most important single requirement for membership is proper quality control facilities. Our by-laws state in part that "...membership is open to firms which manufacture in Canada, under proper conditions for control of quality and standards, pharmaceutical preparations...." In the case of a non-manufacturing subsidiary, then the parent company must meet this requirement. In order to determine the company's qualifications in this respect, 11 of the 21 questions on our membership application form deal with quality control. These are:

10. State name and qualifications of person in charge of control.

11. State name and qualifications of person authorized to release finished products.

12. State number and qualifications of chemists in control department.

13. Broadly describe control laboratory and give approximate floor area.

14. List principal equipment in control laboratory.

15. Check type of laboratory analysis made: a. physiological, b. biological, c. chemical, d. bacteriological.

16. State whether each product batch is identified by code throughout manufacture and distribution.

17. State extent to which raw materials are analyzed to assure their integrity.

18. State extent to which finished products are analyzed to assure their integrity.

19. State extent to which product requiring biological tests are so examined, and state reasons for any omission of such tests.

20. Name those who do outside control work for you and describe it.

When these questions have been answered and submitted by the applicant, the form is then turned over to our Membership Committee for processing. Two Directors are then required to visit the premises of the applicant to determine whether the statements made are correct. If the applicant does not meet these requirements, then he is not eligible for election to membership.

Ethical Responsibility

Applicants for membership are also required to sign an agreement that they will abide by the Principles of Ethics of the Association. These include:

1. The calling of a pharmaceutical manufacturer is one dedicated to a most important public service, and such public service shall be the first and ruling consideration in all dealings.

2. The pharmaceutical manufacturer must produce his preparations only under proper conditions and with scrupulous faithfulness to required standards of quality.

3. Preparations must be labelled and merchandised only in a manner free from misrepresentation, misleading practices of all kinds and in entire harmony with the highest standards of commercial morality and professional ethics.

4. Pharmaceutical manufacturers must constantly and conscientiously strive to advance the science and elevate the calling of manufacturing pharmacy to the highest plane of public value, to the end that it may best and most completely serve the medical profession and the public.

Advertising

On June 15, 1959, our Association adopted an extensive list of "Principles of Ethical Drug Promotion", a copy of which follows. Briefly, this requires that all advertisements of member companies shall contain "complete, conservative and accurate information concerning medicinal agents", and that claims shall not be stronger than warranted by the evidence.

PRINCIPLES OF ETHICAL DRUG PROMOTION

We, members of the Canadian Pharmaceutical Manufacturers Association, recognizing our responsibilities and obligations to promote the public welfare and to maintain honourable relations with the medical and pharmaceutical professions, with associated sciences, and with the public, do pledge ourselves to the following statement of principles:

1. Prompt, complete, conservative and accurate information concerning medicinal agents shall be made available to the medical and pharmaceutical professions;

2. Any statement involved in product promotional communications must be supported by adequate and acceptable scientific evidence. Claims must not be stronger than such evidence warrants. Every effort must be made to avoid ambiguity and implied endorsements. Whenever market, statistical or background information or references to unpublished literature or observations are used in promotional literature, the source must be available to the physical upon request;

3. Quotations from medical literature or from the personal communications of clinical investigators in promotional communications must not change or distort the true meaning of the author;

4. If it is necessary to include comparisons of drugs in promotional communications, either written or verbal, such comparisons must be used only when they are constructive to the physician and made on a sound professional and factual basis. Trade marks are private property that can be used legally only by or with the consent of owners of trade marks;

5. The release to the lay public of information on the clinical use of a new medicinal agent or the new use of an established drug prior to adequate clinical assessment and presentation to the medical profession is not in the best interests of the medical profession or the layman;

6. All medical claims and assertions contained in promotional communications shall have medical review prior to their release.

Any violation of these principles brought to the attention of the General Manager of the Canadian Pharmaceutical Manufacturers Association shall be referred by him to the Board of Directors.

APPENDIX B

MEMBERS

of the

CANADIAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Abbott Laboratories Ltd.,
1350 Cote de Liesse Road,
Montreal, P.Q.

Ames Company of Canada Ltd.,
1131 Bloor Street West,
Toronto 4, Ontario.

Anca Laboratories,
P.O. Box 96, Station "O",
Toronto 16, Ontario.

Anglo-French Drug Company Ltd.,
209 St. Catherine St. East,
Montreal 18, P.Q.

Arlington-Funk Laboratories Div.,
U.S. Vitamin Corp. of Canada Ltd.,
1452 Drummond Street,
Montreal, P.Q.

Astra Pharmaceuticals (Canada) Ltd.,
1004 Middlegate Road,
Cooksville, Ontario.

Ayerst, McKenna & Harrison Ltd.,
P.O. Box 6115,
Montreal, P.Q.

Baxter Laboratories of Canada Ltd.,
P.O. Box 760,
Alliston, Ontario.

Beecham Research Laboratories Ltd.,
P.O. Box 99,
Weston, Ontario.

Bristol Laboratories of Canada Ltd.,
286 St. Paul Street West,
Montreal, P.Q.

The British Drug Houses (Canada) Ltd.,
Barclay Avenue, Queensway,
Toronto 18, Ontario.

Burroughs Wellcome & Co. (Canada) Ltd.,
P.O. Box 159,
Montreal, P.Q.

Calmic Limited,
220 Bay Street,
Toronto, Ontario.

Canada Duphar Limited,
Box 444,
London, Ontario.

Casgrain & Charbonneau Limitee,
445 St. Lawrence Blvd.,
Montreal, P.Q.

Ciba Company Ltd.,
200 Metropolitan Blvd.,
Dorval, P.Q.

Lederle/Cyanamid of Canada Ltd.,
635 Dorchester Blvd. West,
Montreal, P.Q.

Charles E. Frosst & Company,
P.O. Box 247,
Montreal, P.Q.

Geigy Pharmaceuticals,
Division of Geigy (Canada) Ltd.,
2626 Bates Road,
Montreal 26, P.Q.

Glaxo-Allenburys (Canada) Ltd.,
52 Bartor Road,
Weston, Ontario.

J. F. Hartz Company Ltd.,
32-34 Grenville Street,
Toronto 2, Ont.

Hoechst Pharmaceuticals of Canada Ltd.,
3400 Namur Street,
Montreal 16, P.Q.

Hoffman-La Roche Ltd.,
1956 Bourdon Street,
St. Laurent, Montreal, P.Q.

Frank W. Horner Limited,
P.O. Box 959,
Montreal, P.Q.

Ingram & Bell Limited,
256 McCaul Street,
Toronto, Ontario.

Lakeside Laboratories (Canada) Ltd.,
24 Wellington Street West,
Toronto 1, Ontario.

Laurentian Laboratories Ltd.,
442 St. Gabriel Street,
Montreal, P.Q.

Eli Lilly & Company (Canada) Ltd.,
P.O. Box 4037, Terminal "A",
Toronto, Ontario.

Mallinckrodt Chemical Works Ltd.,
378 St. Paul Street West,
Montreal, P.Q.

May & Baker (Canada) Ltd.,
180 Bellarmin Street,
Montreal 11, P.Q.

Mead Johnson of Canada Ltd.,
111 St. Clair Ave. West,
Toronto 7, Ontario.

Merck Sharp & Dohme of Canada Ltd.,
P.O. Box 899,
Montreal, P.Q.

The Wm. S. Merrell Company,
Division of Richardson-Merrell Inc.,
P.O. Box 158,
Weston, Ontario.

Mowatt & Moore Limited,
64 Prince Street,
Montreal, P.Q.

Laboratoires Nadeau Limitee,
100 St. Paul Street West,
Montreal, P.Q.

Ortho Pharmaceutical (Canada) Ltd.,
19 Green Belt Drive, Don Mills,
Toronto 12, Ontario.

Parke Davis & Company Ltd.,
P.O. Box 2100, Station "O",
Montreal, P.Q.

Pfizer Canada,
Division of Pfizer Corporation,
5330 Royalmount Avenue,
Montreal, P.Q.

Pitman-Moore of Canada Ltd.,
E. B. Shuttleworth Division,
14 Dyas Road,
Don Mills, Ontario.

H. Powell Chemical Co. Ltd.,
Bowmanville, Ontario.

Purdue Frederick Company Ltd.,
Terminal Bldg.,
207 Queen's Quay,
Toronto, Ontario.

A. H. Robins Company of Canada Ltd.,
5900 Cote de Liesse,
Montreal 9, P.Q.

Rougier Inc.,
2055 Favard Street,
Montreal, P.Q.

Sandoz Pharmaceuticals,
Division of Sandoz (Canada) Ltd.,
220 Metropolitan Blvd.,
Dorval, P.Q.

W. E. Saunders Limited,
P.O. Box 277,
London, Ontario.

R. P. Scherer Limited,
1370 Argyle Road,
Windsor, Ontario.

Schering Corporation Ltd.,
8370 Labarre Street,
Montreal, P.Q.

G. D. Searle & Co. of Canada Ltd.,
247 Queen Street East,
Brampton, Ontario.

Smith, Kline & French I.A.C.,
300 Laurentian Blvd.,
Montreal, P.Q.

E. R. Squibb & Sons of Canada Ltd.,
P.O. Box 599,
Montreal, P.Q.

Strong Cobb Arner of Canada Ltd.,
575 Niagara Blvd.,
Fort Erie, Ontario.

The Upjohn Company of Canada,
865 York Mills Road,
Don Mills, Ontario.

Henry K. Wampole & Co. Ltd.,
Perth, Ontario.

Warner-Chilcott Laboratories Co. Ltd.,
Division, Warner Lambert (Canada) Ltd.,
727 King Street West,
Toronto 2B, Ontario.

Winthrop Laboratories of Canada Ltd.,
Aurora, Ontario.

John Wyeth & Brother (Canada) Ltd.,
2109 Ottawa Street,
Walkerville, Ontario.

APPENDIX E

ASSISTANCE BY PHARMACEUTICAL MANUFACTURERS

(Excerpts from the Canadian Medical Association Journal, January 1, 1958, through June 30, 1961).

Vol. 78	Vol. No. P	1958 I
C.M.A.J.	78: 1-27	L. Greenberg et al: An immunological study of the Canadian Eskimo. Antigens used were provided by E. Lilly, Lederle, serological tests done by Labor. of Hygiene's Clin. Lab.
"	78: 1-43	J. M. Delage et al: Short Communications: a new Coumarin (Marcumar) Hoffmann-La Roche Ltd. and Solu-Plastin, Frosst.
"	78: 1-62	Meeting of Société Médicale de Montréal: Symposium had collaboration of Lederle.
"	78: 1-66	Wellcome Trust (London) 26,000 Pounds sterling for Cruiser "Floating Research Laboratory".
"	78: 2-85	F. O. Moore: Systemic Mediators of surgical injury. "Assistance" of Winthrop Lab. and Upjohn Co.
"	78: 2-131	L. de Verteuil, H. E. Lehmann: Therapeutic trial of Marsilid in depressed and apathetic patients. "Generous supply of Marsilid", Hoffmann-La Roche Ltd.
"	78: 2-139	A. G. Duncan: Recent advances in dermatological therapy. Various companies have contributed, f.i. Merck, Sharp & Dohme; Upjohn; Squibb, etc.
"	78: 3-187	P. K. Fraser: Penicillin V in the treatment of Streptococcal tonsillitis. E. Lilly supplied Penicillin V pulvules.
"	78: 3-200	J. Wener et al: Clinical experience with a newer non-mercurial oral diuretic - Rolicton. Grant from G. D. Searle, Canada.
"	78: 4-245	I. E. Purkis: The potentiation of obstetric analgesia (Pacatal). Warner & Co. supplied Pacatal.
"	78: 4-63	Benger Prizes to general practitioners.

Vol. 78	Vol. No. P	1958 I (Contd.)
C.M.A.J.	78: 7-63	Benger Laboratories Ltd., Toronto, Ont.
"	78: 5-66 78: 5-61	Lederle Medical Student Research fellowships, (amounts not exceeding $600.00) and Medical Faculty Awards.
"	78: 8-583	A. Bogoch et al: The hyperglycaemic effect of 24-hour i.v. administration of Glycagon in diabetes mellitus. Glycagon supplied by E. Lilly.
"	78: 8-592	J. Wener et al: Chlorothiazide in the management of cardiac cedema. Grant by Merck, Sharpe & Dohme, Montreal.
"	78: 8-614	B. Kanee et al: Clinical & Bacteriological studies on Signemycin Ointment. Signemycin top. ointment supplied by Pfizer, Canada.
"	78: 9-671	E. M. Boyd: The chronic subcutaneous toxicity of Spiramycin Adipate. Grant from Poulenc, Montreal.
"	78: 9-681	A. Hurtig: Occult uterine bleeding. Grant from Canadian Tampax Corp. Ames Co. supplied Hematest and Occultest Tablets.
"	78: 12-944	S. A. Yaffe: Superinfection and systemic moniliasis. Nystatin (Mycostatin) supplied by E. R. Squibb (Canada).
"	78: 12-968	The McGill Diploma course in anaesthesia (Wellcome Trust).
"	79: 8-57 78: 12-51	Awards for experimental Research in problems of aging. Ciba Foundation (London) (Appr. 5 awards 300 Pounds Sterling each).
"	78: 10-801	Pfizer donated a $500. fellowship in hospital pharmacy (for intern).
Vol. 79		1958 II
C.M.A.J.	79: 1-6	G. Cohen: The effect of i.m. Trypsin in chronic bronchitis - Grant by F. W. Horner.
"	79: 1-16	G. C. Large: Crystalline Tetracycline HCL in treatment of chronic and acute maxillary sinusitis Tetracycline (Tetracyn i.v.) donated by Pfizer Co.

C.M.A.J.	79: 3-184	F. Gregoire et al: The treatment of cough by a non-narcotic antitussive. Grant-in-aid by Ciba (Tessalon).
"	79: 3-202	Upjohn scholarships. 12 scholarships ($500. ea.) to the College of General Practice. Each year beginning Jan. 1958 till further notice. Increased to 18, for each province on a numerical basis.
"	79: 5-365	G. O. Dixon et al: Fluothane and other non-explosive halogenated hydrocarbons in clinical anaesthesia. Fluothane supplied by Ayerst, McKenna & Harrison.
"	79: 5-378	W. Garte: The action of Sandostene in atopic dermatitis. Sandostene supplied by Sandoz.
"	79: 5-389	N. Kalant et al: Malignant carcinoid syndrome. Grant by Hoffman-La Roche, Nutley, N.J.
"	79: 5-400	F. Kalz: The effect of Aristocort and Medrol on some skin diseases. Aristocort donated by Lederle Medrol donated by Upjohn Decadron donated by Merck
"	79: 6-468	B. Kanee et al: Long term use of Prednisone in Generalized cases of Lupus erythematosus, scleroderma and neurodermatitis desseminata. Prednisone (Meticorten) supplied by Schering.
"	79: 6-488	C. M. Johnston: Pipadone, a pre-delivery sedative and analgesic. Supplied by Burroughs Wellcome.
"	79: 7-536	H. Van Cauwenberge et al: Haemorrhagic effect of A C T H with anticoagulants. Frosst and Abbott supplied anticoagulants.
"	79: 9-723	C. E. Van Rooyen et al: Ristocetin, a clinical trial. (Spontin supplied by Abbott Lab.)
"	79: 9-748	B. Kanee et al: The use of Triamcinolone (Aristocort) in selected dermatoses. Aristocort supplied by Lederle Laboratories.
"	79: 10-843	M. K. Lane et al: Tests for proteinuria. Albutest & Albustix supplied by Ames Co.

C.M.A.J.	79: 11-881	E. Bolte et al: Studies on new diuretic compounds: Spirolactone & Chlorothiazide Spirolactone & Diuril supplied by Searle (Chicago) & Merck (Montreal). Reserpine & Apresoline (Ciba), Inversine (Merck), Ansolysen (Poulenc), Sustagen (Mead Johnson).
"	79: 11-891	L. J. Harris et al: The effect of Nystatin (Mycostatin)on neonatal candidiasis. Grant by Squibb International Division. Supplied also Mycostatin solution.
"	79: 11-897	W. Leith et al: The use of Preludin in the obese diabetic. (Preludin supplied by Geigy Pharmaceuticals.)
"	79: 11-917	J. H. Harvey et al: Clinical study of Cadmium sulfide shampoo. Grant-in-aid Pitman Moore Co. (Indianapolis).
"	79: 11-918	F. Kalz et al: Vitamin A serum levels after digestion of different vitamin A preparations. Grant by Hoffman-La Roche Ltd., Canada who also supplied Vitamin A drops and dragees.
"	79: 11-924 930 930-32	Report on the medical section in the Canadian Pharmaceutical Industry. "Support to pure as well as to applied research" (W. Penfield).
"	79: 12-978	J. N. Fortin et al: A psychosomatic approach to the pre-menstrual tension syndrome. Grants from Purdue Frederick (N.Y.) and Ciba (Montreal).
"	79: 12-985	N. L. Mason-Browne: Perphenazine in practice. (Trilafon supplied by Schering, Montreal).
"	79: 12-988	O. Kofman: Experience with Reserpine (Serpasil) and Perphenazine (Trilafon) in acute alcoholic intoxication and alcoholic psychosis. (Serpasil supplied by Ciba, Trilafon by Schering).
"	79: 12-992	J. G. Sussex: Sulfaphenazol (Orisul) in urology. Grant-in-aid and supply of Orisul by Ciba.
Vol. 80		
C.M.A.J.	80: 2-125	A. L. Hudson: A new drug for control of itching (trimeprazine). Trimeprazine supplied by Poulenc, Canada.

C.M.A.J.	80: 3-189	E. V. Shute: Alpha Tocopherol in the management of Chronic Phlebitis and the Post-Phlebitic syndrome. Alpha Tocopherol supplied by Webber Pharmaceuticals Ltd., Toronto.
"	80: 3-194	D. C. Turk: Laboratory studies of a multiple-antibiotic spray. Polybactrin supplied by Calmic Ltd., England and Pfizer Ltd., England.
"	80: 4-245	C. E. Robinson et al: Triamcinolone in rheumatoid arthritis. Aristocort was supplied by Lederle.
"	80: 4-266	J. Sternberg et al: Metabolic studies in atherosclerosis. Grant from Webber Pharmaceuticals Ltd., Toronto.
"	80: 4-291	E. Bolte et al: Mental depressive episodes during Rauwolfia therapy for arterial hypertension, with special reference top dosage. Rauwolfia preparations supplied by Ciba (Serpasil), Serpiloid, Rauwiloid by Ricker Lab., Raudixin by Squibb.
"	80: 5-346	M. Lefebvre et al: Triacetyloleandomycin (supplied by Pfizer, Canada).
"	80: 5-359	P. O. O'Reilly et al: Sustained - release Nicotinic acid (Nicospan) - Supplied by Merrell.
"	80: 6-448	J. H. Harvey, F. Kalz: Alteration of wheal resorption time by intravenous use of an antihistaminic drug and a calcium salt. Grant given by Sandoz (Canada).
"	80: 7-535	H. Azima: Imipramine (Tofranil) a new drug for the depressed. Assistance of Geigy. N.I.M.H. Grant.
"	80: 7-540	R. B. Sloane et al: The use of Imipramine (Tofranil) for depressive states in open ward settings of a General Hospital: a preliminary report. Tofranil supplied by Geigy.
"	80: 7-546	M. Straker: Imipramine (Tofranil) a safe effective anti-depressant drug in private practice. Tofranil supplied by Geigy.

C.M.A.J.	80: 8-629	J. L. Cohen et al: Pustular acne, Staphyloderma and its treatment with tolbutamide. Mobenol supplied by F. W. Horner.
"	80: 9-719	J. Lavoie et al: A new colonic evacuant Bisacodyl (dulcolax) supplied by Geigy.
"	80: 9-734	D. W. Archibald et al: The evaluation of a cough suppressant: an exercise in clinical pharmacology (Prep. 10611) Grant from Ciba.
"	80: 10-773	J. B. R. McKendry et al: Clinical experience with DBI (Phenformin) in the management of diabetes. DBI supplied by Arlington-Funk Laboratories.
"	80: 10-785	W. F. Connell et al: Evaluation of anticoagulant therapy with anisindione (Miradon). Grants from Schering Corp., Montreal, Heparin from Connaught, Toronto.
"	80: 10-826	G. Nadeau et al: Estimation of phenothiazine derivatives (especially Chlorpromazine and Levomepromazine) in urine. Drugs supplied by Poulenc.
"	80: 10-843 842	Purdue Frederick Medical achievement Travel award. Lecture series by courtesy of Charles E. Frosst & Co. New Laboratory, gastrointestinal research. Grant from Abbott Laboratories to Royal Victoria Hospital.
"	80: 11-880	J. R. Taylor: Intravenous and oral trial of stilboestrol diphosphate in prostatic carcinoma. Honvol supplied by F. W. Horner.
"	80: 11-885	V. Panaccio: Trimeprazine, a new phenothiazine derivative for treatment of pruritic dermatoses. Panectyl supplied by Poulenc.
"	80: 11-913 80: 11-1002 80: 11-1003	College of General Practice annual assembly: 18 & 10 bursaries to aid post graduate courses, provided by Schering and Upjohn. Wyeth postgraduate education fund $7,500.00. Mead-Johnson grant of $5,000.00 to research committee.
"	80: 11-963	A. B. Kerenyi et al: The use of intravenous Methylphenidate (Ritalin) in psychiatric interviewing. Ritalin supplied by Ciba.

Vol. 80		1959 (Contd.)
C.M.A.J.	80: 11-968	L. Lamoureux et al: Preliminary clinical study of dipipadone hydrochloride (Pipadone) in anaesthesia. Financial help by Burroughs Wellcome.
Vol. 81		1959 II
C.M.A.J.	81: 1-1	J. C. Wilt et al: Poliomyelitis in Manitoba 1958. Supported by Connaught Research Laboratories.
"	81: 1-9	D. P. Schwartz: Chlorothiazide in the prenatal outpatient: a study of its effects upon serum electrolytes. Diuril supplied by Merck & Co., Westpoint, Pa.
"	81: 1-43	P. Payne: Trifluoperazine in treatment of the acutely ill psychotic. Stelazine supplied by Smith Kline & French.
"	81: 1-67	Grant from Mead Johnson $3,500.00 for research in enzyme deficiencies in the newborn.
"	81: 2-101	T. W. Davies et al: Experience with Glipasol (R.P.2259) - an antidiabetic sulfonamide drug. Grant from Poulenc, Montreal.
"	81: 2-123	Pharmacology Society Symposium. Study made jointly by Frosst and Ciba Companies in Montreal on the toxicity of reserpine.
"	81: 3-159	H. Schwartz: The comparative effects of corticotrophin (ACTH) and steroids in hormonal treatment. Supply of Duracton by Nordic Biochemicals Ltd.
"	81: 3-165	A. R. Birt et al: Griseofulvin in the oral treatment of tinea capitis. Griseofulvin supplied by Glaxo-Allenburys (Canada).
"	81: 3-173	A. Flint et al: Griseofulvin a new oral antibiotic for the treatment of fungous infections of the skin. Grisovin supplied by Glaxo (Unik, Que.)
"	81: 4-221	J. Wener et al: Hydrochlorothiazide (Hydrodiuril) in the management of cardiac oedema. Grant from Merck Sharp & Dohme.
"	81: 4-231	R. V. Chapple et al: The present status of the clinical evaluation of Fibrinolysin. Fibrinolysin supplied by Ortho Research Foundation, Raritan, N.J.

C.M.A.J.	81: 5-383	G. D. Howden: The successful treatment of a case of central retinal vein thrombosis with intravenous fibrinolysin. Fibrinolysin supplied by Ortho Research Foundation, Raritan, N.J.
"	81: 7-546	J. M. Huot et al: Levomepromazine (Nozinan) a new neuroleptic agent for treatment of senile patients. All medications supplied by Poulenc.
"	81: 8-658	G. Nadeau et al: Estimation of Phenothiazine derivatives in urine. Largactil and Nozinan supplied by Poulenc, Ketodase by Warner-Chilcott, Toronto.
"	81: 9-717	G. J. Sarwer-Foner et al: Clinical investigation of Stelazine in open psychiatric settings. Stelazine supplied by Smith Kline & French.
"	81: 9-724	C. H. A. Walton: Clinical experience with dexamethasone. Decadron supplied by Merck Sharp & Dohme.
"	81: 9-726	W. D. Stewart et al: Griseofulvin, clinical report. Grisovin supplied by Glaxo-Allenburys (Canada) Ltd.
"	81: 11-933	K. A. Baird: A Promethazine-Ephedrine combination for relief of respiratory allergies. Phenergan-Ephedrine supplied by Poulenc.
"	81: 11-945	College General Practice - 18 Upjohn Scholarships. $500.00 each for 1960. Ten Bursaries $500.00 each by Schering.
"	81: 12-984	A. Rapoport et al: Some Short-term Metabolic effects of Chlorothiazide in Hypertensives on a rice diet. Diuril supplied by Merck Sharp & Dohme.
"	81: 12-991	G. J. Sarwer-Foner et al: Depressive states and drugs. II Study of Phenelzine Dihydrogen sulfate (Nardil) in open Psychiatric settings. Nardil supplied by Warner-Chilcott Laboratories.
"	81: 12-1009	A. B. Dobkin e al: Micoren in Barbituate poisoning. Micoren supplied by Geigy.

Vol. 82 — 1960 I

C.M.A.J.	82: 4-179	G. Gilbert et al: Treatment and prevention of Rheumatic Carditis. Bicillin supplied by John Wyeth & Brother.
"	82: 4-195	C. E. Boyde et al: Penicillin vomiting. Grant from Parke Davis.
"	82: 6-311	N. A. Hinton et al: The effect of combinations of antibiotics on coagulase-positive Staphylococci. Pfizer supplied certain of the antibiotics.
"	82: 8-418	G. M. Berneske et al: Clinical trial of high dosage Vitamin E in human muscular dystrophy. Vitamin E was supplied by Webber Pharmaceuticals.
"	82: 15-767	H. Reed: Chymotrypsin in cataract surgery. Chymotrypsin supplied by Armour (Chicago) and Nova Drug Co., Montreal supplied Ophthalmic Quimotrase.
"	82: 16-825	D. A. Kavelman: Bemegride in the treatment of acute sedative intoxication. Bemegride supplied by Abbott, Montreal.
"	82: 16-833	F. Kalz et al: The use of Promethazine as a local anaesthetic. Phenergan supplied by Poulenc.
"	82: 17-872	J. Genest et al: Studies on a new Hypotensive agent: Bretylium Tosylate. Grant from Burroughs Wellcome & Co.
"	82: 19-953	K. I. Pearce: Elipten, a clynical evaluation of a new anticonvulsant. Elipten supplied by Ciba Co.
"	82: 2-1005	W. Graham: The status of G-27202 (Metabolite 1 of Phenylbutazone) in the treatment of rheumatic disorders. Drug supplied by Geigy.
"	82: 20-1031	L. Levy et al: The use of Nardil in depression. Nardil supplied by Warner-Chilcott.
"	82:24-1219	R. Desmeules et al: Phenylbutazone and Isoniazid in pulmonary tuberculosis. Butazolidin supplied by Geigy.

Vol. 82		1960 I (Contd.)
C.M.A.J.	82: 25-1275	G. Angioli: Combined use of Nystatin and antituberculous drugs in the management of coexistent fungal-tuberculous infections. Grant by Squibb.
Vol. 83		1960 II
C.M.A.J.	83: 3-102	T. W. Davis et al: Hepatitis caused by Glipasol, an antidiabetic sulphonamide drug. Glipasol supplied by Poulenc. Grant by Poulenc.
"	83: 8-355	M. Aronovitch et al: The continuous alternating Chemotherapy of cancer. Merck and Co., Ayerst McKenna, Pfizer, F. W. Horner supplied various drugs. Prednisone supplied by Schering.
"	83: 8-387	L. Mandel et al: Bisacodyl (Dulcolax) an evacuant suppository. Grant-in-aid by Geigy.
"	83: 9-452	Wellcome Trust (London) donates 70,000 Pounds for research accommodations of the Ch. H. Best Institute.
"	83: 10-533	E. J. Cleveland et al: Home treatment of depression with Tofranil. Tofranil supplied by Geigy.
"	83: 11-567	R. L. McMillan: Long term anticoagulant therapy after myocardial infarction. Dicoumarol tablets supplied by Abbott.
"	83: 11-620	Warner-Lambert Pharm. fellowship $1,500.00 "for promotion of Canadian education and research in pharmacy and medicine."
"	83: 13-691	G. Pigeon et al: Guanethidine (Ismelin) administration in 28 Hypertensive patients. Grant by Ciba, also supplied drugs.
"	83: 14-743	G. Pigeon et al: Prolonged Hydralazine HCl administration in 132 hypertensive patients. Help and supply of Apresoline by Ciba.
"	83: 14-747	H. Z. Movat: Pathology and Pathogenesis of the diffuse collagen diseases.
"	83: 15-797	Lecture series "Collagen diseases" sponsored by Charles E. Frosst & Co.

C.M.A.J.	83: 15-781	The evolution of Rheumatic heart disease in children. Five year report of a co-operative clinical trial of ACTH, CORTISONE AND ASPIRIN. Funds provided by Armour Laboratories and Merck & Co.
"	83: 16-836	J. F. L. Woodbury et al: Effectiveness of Methyl-prednisolone Tertiary-Butylacetate intra-articularly in rheumatoid arthritis. Drugs supplied by Upjohn and Merck Co.
"	83: 16-839	J. C. Wilt et al: Enterovirus infections in Manitoba - 1959. Financial support from Connaught Medical Research Laboratories.
"	83: 17-881	J. A. MacDonald et al: Meconium ileus: an eleven year review of the Hospital for Sick Children, Toronto, Ont. Anturan supplied by Geigy, Flexin supplied by McNeil Laboratories.
"	83: 17-894	J. A. McLean et al: A summary of experience with Alpha Chymotrypsin at the Vancouver General Hospital. Zonulyn supplied by British Drug Houses (Canada).
"	83: 18-933	L. Campeau et al: Treatment of Bacterial Endocarditis: a review of 35 cases. Antibiotics supplied by Pfizer, Wyeth, Abbott.
"	83: 18-948	A. L. Jones et al: Use of Thioridazine (Mellaril) in a variety of clinical settings. Assistance and supply of Mellaril by Sandoz.
"	83: 19-979	M. L. Barr et al: Sex Chromatin, Sex Chromosomes and sex anomalies. Colcemid donated by Ciba.
"	83: 19-991	A. Branch et al: Clinical and laboratory experiences with a new Synthetic Penicillin-2, 6-Dimethoxyphenyl Penicillin. Drug provided by Bristol Lab.
"	83: 19-997	M. Aronovitch et al: Use of Cyclophosphamide in advanced malignancies. Drug supplied by F. W. Horner.
"	83: 21-1088	H. Roberts et al: Use of Alphaprodine and Levallorphan during labour. Hoffman-La Roche contributed to the research fund and supplied drugs.

C.M.A.J.	83: 21-1093	D. J. Morris et al: Human Biossay of a new anti-tussive agent. Study supported by G. D. Searle & Co., Chicago.
"	83: 23-1224	Benger Laboratories Ltd., Prizes of $100. - each for the five best essays.
"	83: 24-1249	A. B. Kerenyi et al: Depressive states and drugs, use of Methylphenidate (Ritalin) in open psychiatric settings and in office practice. Ritalin supplied by Ciba.
"	83: 25-1289	H. P. Higgins et al: Use of an aldosterone antagonist in the diagnosis of primary Hyper-aldosteronism. Aldactone supplied by G. D. Searle & Co., Chicago.
"	83: 25-1295	P. M. O'Sullivan: Topical Corticosteroid therapy in ulcerative colitis. Solucortef and Solumedrol supplied by Upjohn Co.
"	83: 25-1298	E. M. Boyd: Chlophedianol Hydrochloride: a new anti-tussive agent. Grant-in-aid from Schenlabs Pharmaceuticals Ltd.
"	83: 25-1306	M. Straker: Clinical evaluation of a new anti-depressant agent: Tranylcypromine with trifluoperazine (Parstelin). Parstelin supplied by Smith Kline & French.
"	83: 25-1321	J. W. Gerrard et al: Glutamic acid derivatives in juvenile and adult celiac disease. Lederle award for assistance in this project.
"	83: 26-1379	G. B. Sexton: Local injection of triamcinolone Acetonide in the management of certain skin conditions. Kenalog Parenteral supplied by E. R. Squibb, N.Y.
"	83: 26-1381	E. Mankiewicz: In vitro susceptibility of M. Tuberculosis and of a typical acid-fast Bacteria to Ethionamide (TH 1314). "Assistance" by Poulenc.
"	83: 26-15	Wellcome Trust (London) $108,000. to McGill University.

C.M.A.J.	84: 2-91	D. S. Beanlands et al: Therapeutic trial of a new oral diuretic. Grant from Geigy.
"	84: 3-152	V. A. Kral: The use of Mellaril in aged people. Mellaril supplied by Sandoz.
"	84: 4-183	J. A. Lewis: Guanethidine-Report of a clinical trial. Guanethidine supplied by Ciba. Pempidine supplied by Ayerst McKenna & Harrison.
"	84: 4-187	G. R. Cumming et al: Guanethidine as the sole agent in the treatment of hypertension. Guanethidine supplied by Ciba. Bretylium tosylate supplied by Burroughs Wellcome Company.
"	84: 4-213	L. W. Woods et al: Use of Nardil in a General Hospital setting. Nardil supplied by Warner-Chilcott.
"	84: 5-251	N. Kalant et al: The effect of an atherogenic diet on normal and alloxandiabetic rats. Grant from Ciba. Sodium choleate supplied by Ames Co. Ind. Cholestrol supplied by Merck & Co. Ltd., Montreal.
"	84: 5-263	M. Aronovitch et al: Some clinical and experimental studies with Viomycin. Grant from Ciba.
"	84: 5-268	W. Hughes: A comparative evaluation of two Phenothiazines in the management of chronic Schizophrenia. Drugs donated by Sandoz and Smith, Kline & French.
"	84: 7-374	J. A. Aguilar et al: Aminoglutethimide in the treatment of epilepsy. Elipten supplied by Ciba.
"	84: 8-403	J. Genest: Angiotensin, Aldosterone and human arterial hypertension. Supported by Ciba, drugs supplied.
"	84: 9-484	F. Kalz et al: Use of local injections of corticosteroids into cutaneous lesions. Depo-Medrol donated by Upjohn Co. Ltd.

C.M.A.J.	84: 10-535	L. Campeau: Treatment of bacterial endocarditis by oral phenethicillin potassium (Syncillin). Syncillin supplied by Bristol, Canada.
"	84: 11-584	G. W. Korn: The use of Norethynodrel (Enovid) in clinical practice. Help of G. D. Searle.
"	84: 12-662	M. A. Gard et al: Factors influencing the incidence of sore throat following endotracheal intubation. Drugs supplied by Abbott.
"	84:16-873	D. H. Carr et al: A probable XXYY sex determining mechanism in a mentally defective male with Klinefelter's Syndrome. Colcemid donated by Ciba.
"	84: 19-1059	An objective assessment of the effects of Nialamide on depressed patients. Niamid supplied by Pfizer.
"	84: 19-34	Ciba Medical Research Fellowship for 1961. (Thyroid Physiology).
"	84: 20-1124	H. G. Kelly et al: Renal and Cardiovascular effects induced by intravenous infusion of Magnesium Chelate. Magnesium Chelate supplied by Geigy.
"	84: 20-1116	A. M. Edwards et al: Observations on Juvenile Hypothyroidism in Native Races of Northern Canada. Thyroid-Stimulating Hormone supplied by Nordic Pharmaceutical.
"	84: 22-1259	T. A. Ban: A comparative clinical study on three Hypnotic drugs. Drugs provided by Neo-Drug Company. Wm. S. Merrell Co. supplied Kevadon.